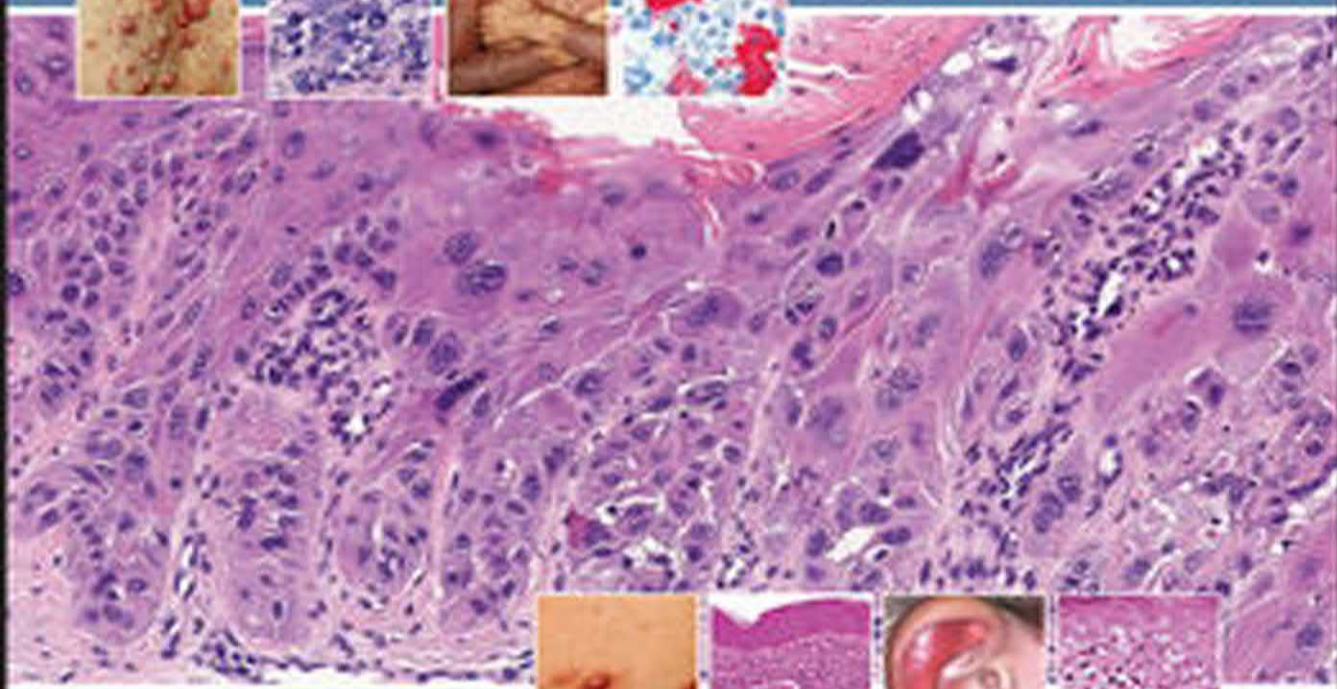


ATLAS OF DERMATOPATHOLOGY



TUMORS, NEVI, AND CYSTS

Günter Burg

Heinz Kutzner, Werner Kempf
Josef Felt, Bruce R. Smoller

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**Atlas of Dermatopathology: Tumors,
Nevi, and Cysts**

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Atlas of Dermatopathology

Tumors, Nevi, and Cysts

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To our families and teachers, who have supported and guided us

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Preface

In tumorous processes, the typical cytomorphology and growth pattern assessed by histological examination are the major hallmarks of correct diagnosis. Therefore, this text-atlas, in 13 well-illustrated chapters, presents the major cytomorphological elements of the skin, and describes the histological characteristics of epidermal and organoid nevi, hamartomas and tumors of the epidermis, adnexal structures, melanocytic lesions, and tumors of connective tissue, vessels, fat, muscles, nerves, mast cells, histiocytes, and hematopoietic cells, i.e. lymphomas and leukemias. In addition to the histology, the clinical features and differential diagnoses (DD:) are presented for each entity. As cysts may be clinically misdiagnosed as tumorous lesions, a chapter on cysts has been added for differential diagnostic purposes.

The text of the clinical features (Cl:) is given in prose form, whereas the description of the histological features (Hi:) follows the approved bullet point style in order to keep the information as compact and concise as possible.

Some of the diagnoses listed lack clinical or histological pictures.

Even though we have tried to cover most common diagnoses, the book is far from being comprehensive. Many variants of tumors described in the literature are waiting to be included in the next edition and may be studied in special books dealing with distinct adnexal, vascular, soft tissue, hematopoietic or other neoplasias.

Günter Burg, Heinz Kutzner, Werner Kempf,
Josef Feit, Bruce R. Smoller
2018

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CHAPTER 1

Epidermis

CHAPTER MENU

Nevi

Epidermal Nevus

Variant: Inflammatory Linear Verrucous Epidermal
Nevus (ILVEN)

Keratoses

Seborrheic Keratosis (SK) and Variants

Confluent and Reticulate Papillomatosis (Gougerot
and Carteaud)

Reticulate Pigmented Anomaly of the Flexures
(Dowling–Degos Disease)

Acanthosis Nigricans

Solar (Actinic) Keratosis

Cornu Cutaneum

Acanthomas, Non-Viral

Solar Lentigo

Callus, Factitial Acanthoma

Knuckle Pads (Chewing Pads)

Pale (Clear) Cell Acanthoma

Large Cell Acanthoma

Acantholytic Acanthoma

Warty Dyskeratoma

Porokeratoma (Porokeratosis Mibelli)

Acanthomas, Viral

Verruca Vulgaris

Bowenoid Papulosis

Acrokeratosis Verruciformis (Hopf)

Molluscum Contagiosum

“Pseudocarcinomas” and Neoplasms with Intermediate

Malignant Potential

Keratoacanthoma (KA)

Epithelioma Cuniculatum (Verrucous Carcinoma) (ECVC)

Papillomatosis Cutis Carcinoides

Florid Papillomatosis of the Oral Cavity (Oral Verrucous
Carcinoma)

Buschke–Löwenstein Tumor (Giant Condyloma)

Malignant Epidermal Neoplasms

Bowen’s Disease (Carcinoma *in situ*)

Basal Cell Carcinoma (BCC)

Syndromatic BCC (Basal Cell Nevus Syndrome,
Gorlin–Goltz)

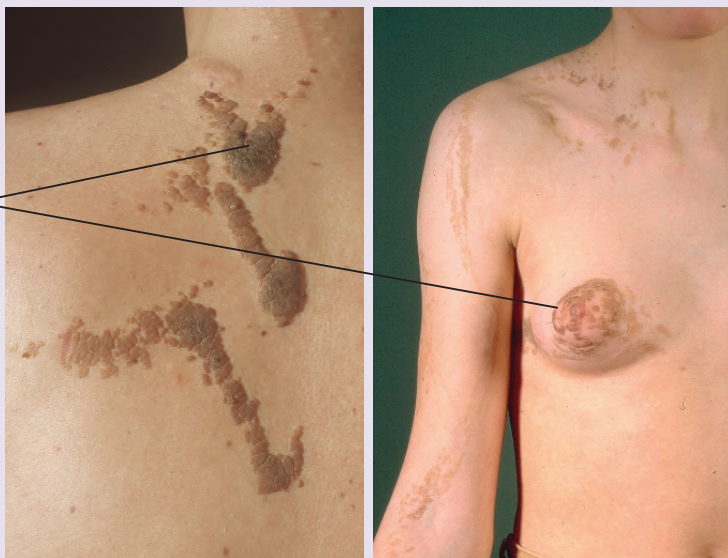
Fibroepithelioma of Pinkus

Squamous Cell Carcinoma (SCC)

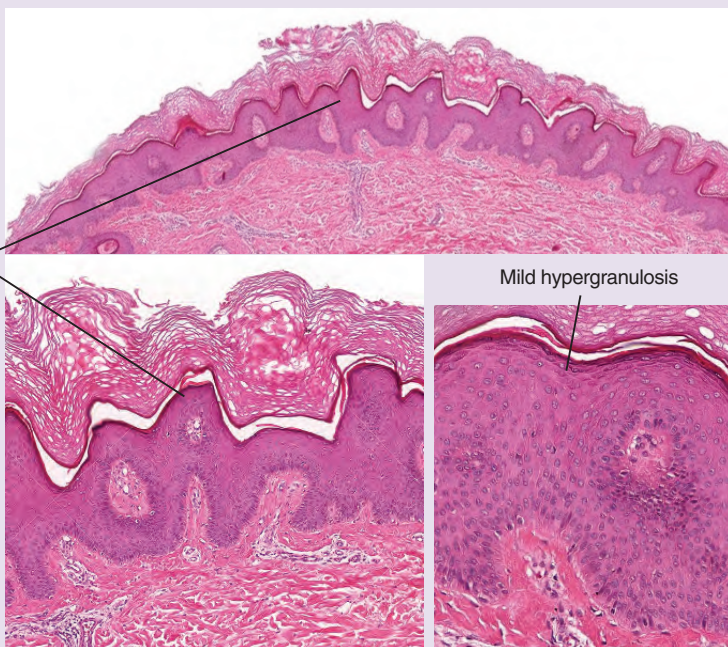
Nevi

Epidermal Nevus

Hyperkeratotic streaks or plaques



Psoriasiform hyperkeratosis, acanthosis and papillomatosis



Cl: Epidermal nevi are the most common manifestations of cutaneous mosaicism. They are autosomal dominant segmental hyperkeratotic verrucous or papular lesions present at birth. They present

as brown or gray isolated, linear, zosteriform, or whorled patches or follow Blaschko lines.

Hi: Psoriasiform acanthosis, papillomatosis, orthohyperkeratosis.

DD: Seborrheic keratosis; epidermolytic hyperkeratosis.

Reference

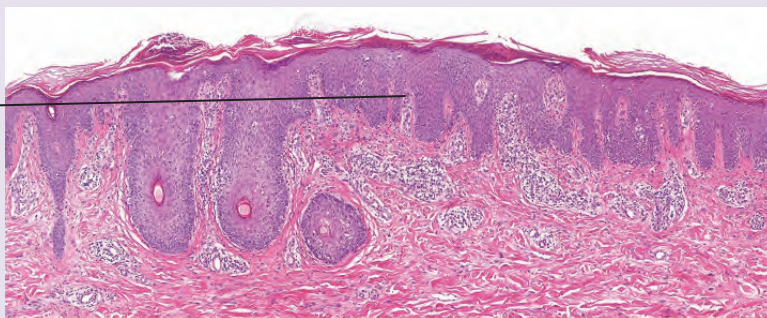
Chi, C.C., Wang, S.H., and Lin, P.Y. (2009) Combined epidermal-connective tissue nevus of proteoglycan (a type of mucinous nevus): a case report and literature review. *J Cutan Pathol* **36**(7): 808–11.

Variant: Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)

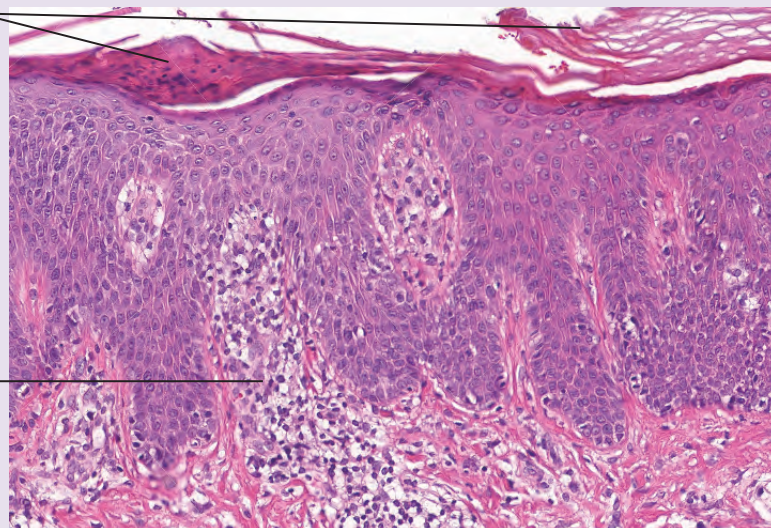
Inflammatory
verrucous
linear lesions



Psoriasiform
acanthosis
and
papillomatosis



Alternating
ortho- and
parakeratosis



Inflammatory
infiltrate

SEBORRHEIC KERATOSIS AND VARIANTS

CI: ILVEN is considered a variant of epidermal nevus. It shows linear verrucous streaks with inflammatory erythema, scaling, and pruritus.

Hi:

- Psoriasiform acanthosis and papillomatosis
- Alternating areas of ortho- and parakeratosis
- Decreased to absent granular layer
- Prominent acantholysis in some cases
- Inflammatory infiltrate in the papillary dermis

Keratoses

Seborrheic Keratosis (SK) and Variants

Most common epidermal tumor. Synonyms: Senile keratosis, seborrheic wart. Even though resembling common warts, there is no association with human papilloma virus (HPV). They are benign but cosmetically disturbing, sometimes irritated, and occasionally are confused with pigmented tumors like malignant melanoma or pigmented basal cell carcinoma.

CI: Seborrheic keratosis may present various clinical features. The most common variants are

acanthotic seborrheic keratoses, which occur as multiple elevated light or dark brown lesions of various sizes preferentially on the trunk, head, and neck of elderly people, sparing palms and soles. *Flat seborrheic keratoses* are referred to as solar lentigo in sun-exposed areas. Others are *papillomatous* and hyperkeratotic with a cerebriform surface. They may be inflamed (*irritated* or “activated”). *Melanoacanthoma* is a dark pigmented seborrheic keratosis in elderly people, which may be confused with malignant melanoma. *Dermatosis papulosa nigra*, preferentially occurring in the sub-orbital and temporal region of black and dark-skinned individuals, presents as tiny pigmented papules. *Reticulated adenoid* (pigmented) and *clonal* (intraepidermal, Borst–Jadassohn) seborrheic keratosis or SK with “monster cells” are distinct histological features without special clinical presentation. Hyperkeratotic SK (*stucco keratoses*) appear as tiny multiple whitish hyperkeratotic lesions like gypsum splatters on the dorsum of hands, feet, and lower legs.

DD: Verruca vulgaris; acrokeratosis verruciformis (Hopf).

Variant: Acanthotic Seborrheic Keratosis



Multiple seborrheic keratoses on the trunk



Flat (above) and papillomatous (below) seborrheic keratoses

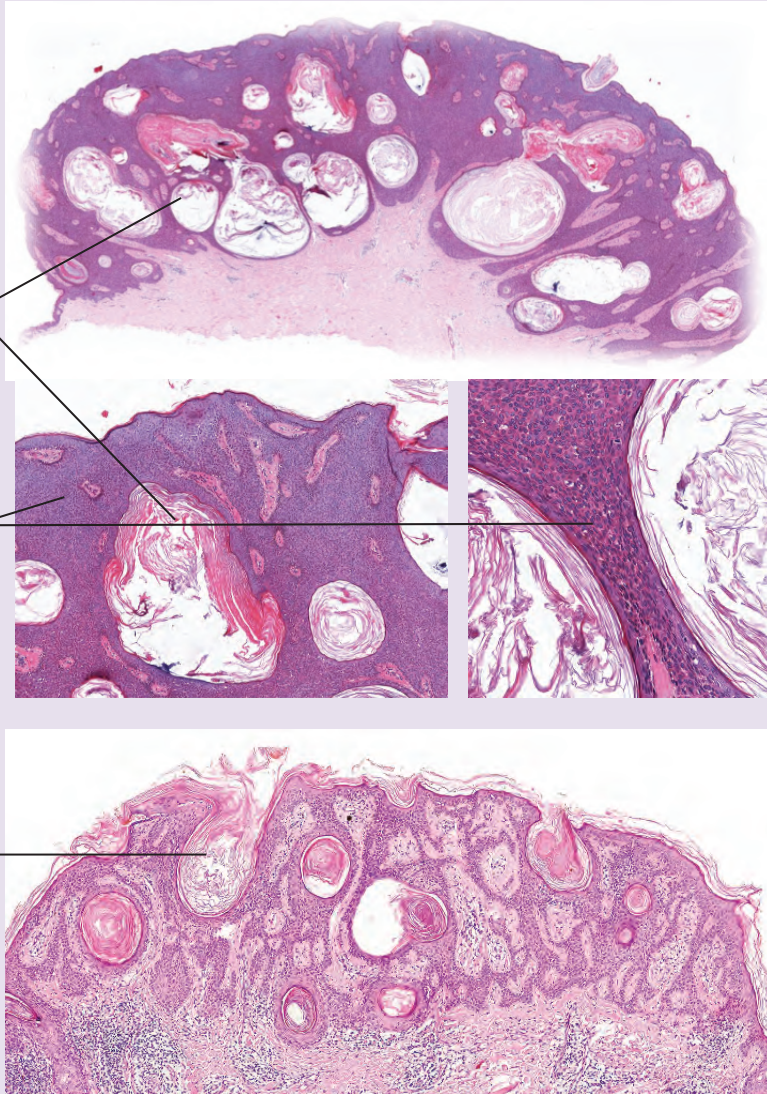
SEBORRHEIC KERATOSIS AND VARIANTS**Variant: Acanthotic Seborrheic Keratosis**

Psoriasiform
acanthosis and
papillomatosis

Horn-filled
pseudocysts

Acanthosis
consisting of
basaloid cells

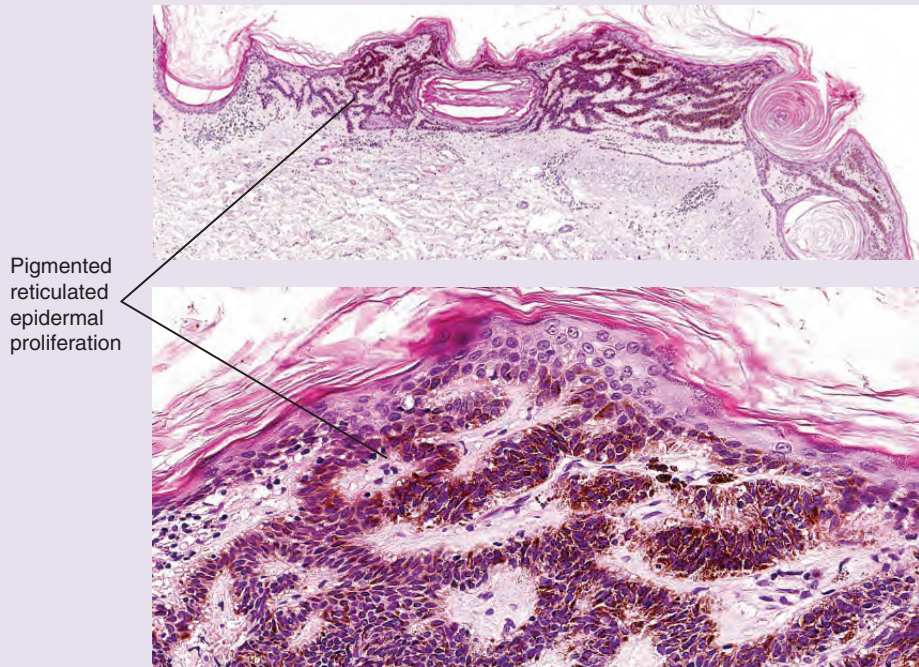
Horn-filled
pseudocysts



Hi: Broad acanthotic epidermis composed of basaloid cells. Anastomosing horny pseudocysts filled with keratin.

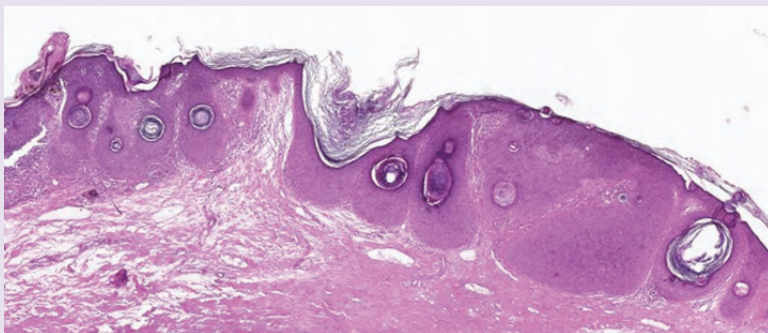
SEBORRHEIC KERATOSIS AND VARIANTS

Variant: Reticulated, Pigmented Seborrheic Keratosis



Hi: Anastomosing small epithelial cords mostly with basal pigmentation forming a reticular net.

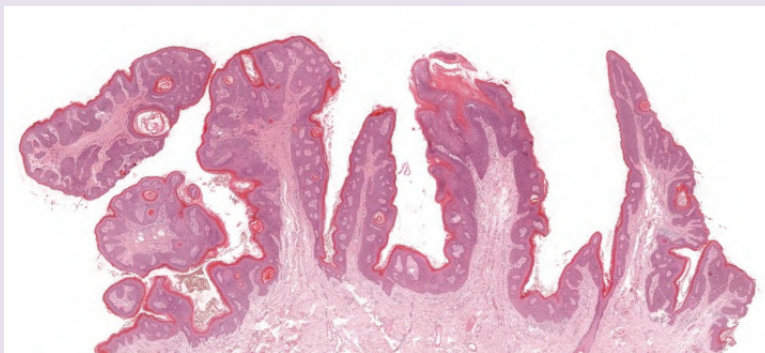
Variant: Flat Seborrheic Keratosis



Hi: Flat plump acanthosis with keratin-filled horny pseudocysts.

SEBORRHEIC KERATOSIS AND VARIANTS

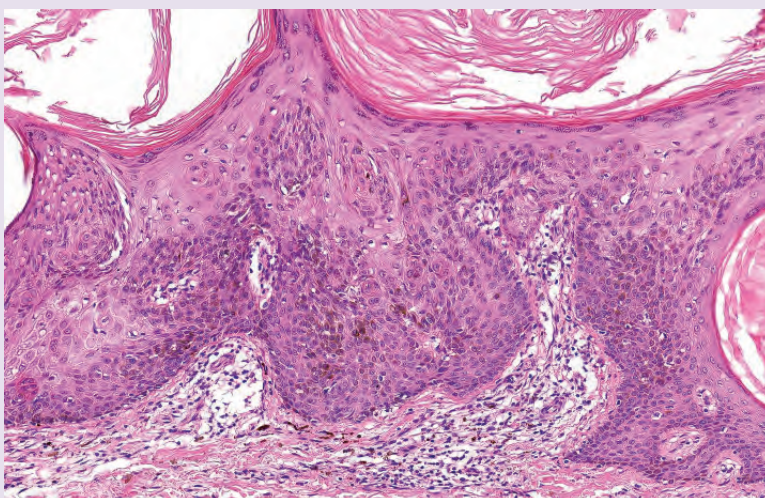
Variant: Papillomatous Seborrheic Keratosis



Hi:

- Church spire-like proliferations
- Papillomatosis
- Ortho- and parakeratosis

Variant: Activated (Irritated) Seborrheic Keratosis



Hi: Mixed cellular inflammatory infiltrate in the upper dermis and between rete ridges.

Variant: Dermatitis Papulosa Nigra

CI: Multiple tiny black papules in almost 50% of black-skinned individuals, commonly located on the cheeks and periorbital region. They resemble small seborrheic keratosis.

Hi: Corresponds to flat or reticulated pigmented seborrheic keratosis.

DD: Small seborrheic keratosis; fibromas.

Reference

Grimes, P.E., Arora, S., Minus, H.R., and Kenney, J.A. Jr (1983) Dermatitis papulosa nigra. *Cutis* **32**(4)L 385–6, 392.

SEBORRHEIC KERATOSIS AND VARIANTS

Variant: Dermatosi Papulosa Nigra

Variant: Melanoacanthoma (Pigmented Seborrheic Keratosis)

Tiny pigmented papules

Variant: Dermatosi Papulosa Nigra

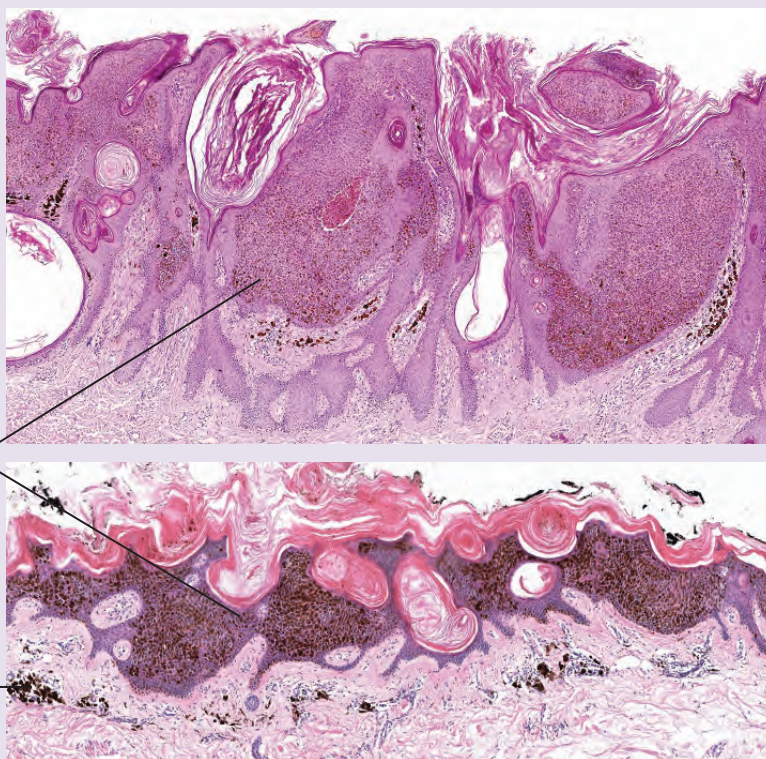


Variant: Melanoacanthoma (Pigmented Seborrheic Keratosis)

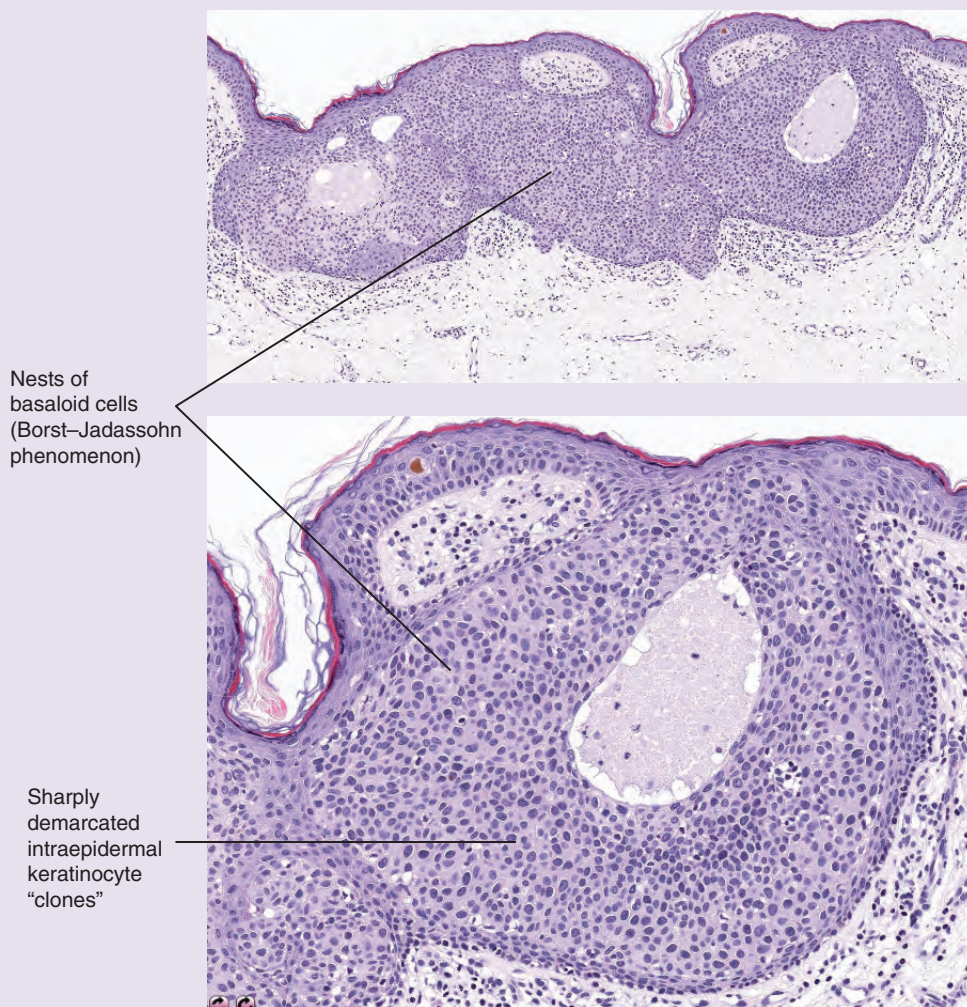


Acanthotic epidermis with pigmentation

Clusters of melanophages



Hi: Deeply pigmented variant of acanthotic seborrheic keratosis, consisting of a mixture of pigmented keratinocytes and dendritic melanocytes.

SEBORRHEIC KERATOSIS AND VARIANTS**Variant: Clonal (Intraepidermal) Seborrheic Keratosis (Borst–Jadassohn)**

Hi: Intraepidermal clonal accumulation of epidermal cells, sometimes demarcated by stronger pigmentation.

DD: Hidroacanthoma simplex (eccrine poroma); clonal Bowen disease; intraepidermal squamous cell carcinoma.

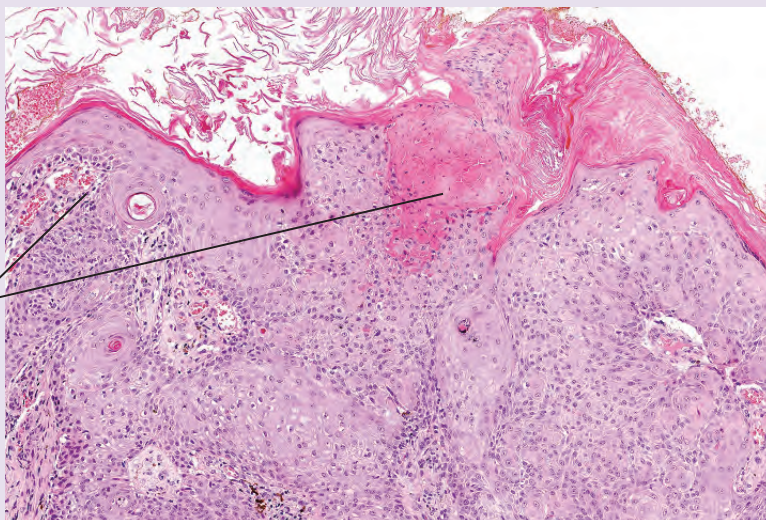
Reference

Lora, V., Chouvet, B., and Kanitakis, J. (2011) The "intraepidermal epithelioma" revisited: immunohistochemical study of the Borst–Jadassohn phenomenon. *Am J Dermatopathol* **33**(5): 492–497.

SEBORRHEIC KERATOSIS AND VARIANTS

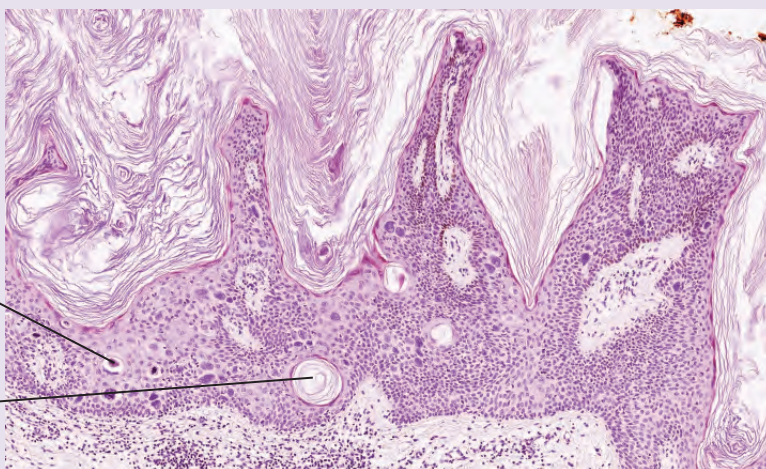
Variant: Seborrheic Keratosis with Monster Cells (Bowenoid)

Inflammation,
dilatation
of vessels,
and exudate



Monster cells

Broad epidermis
composed of
basaloid cells.
Horn-filled
pseudocyst



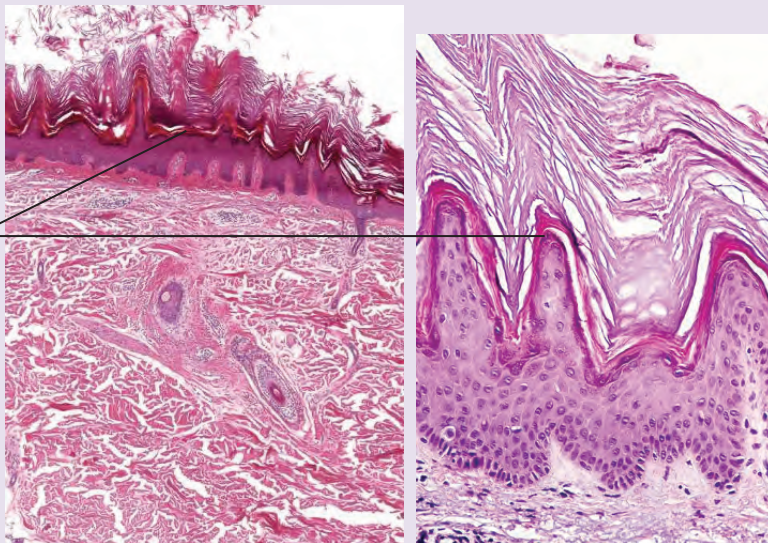
Hi: Morphological variant of SK with scattered large, haloed cells.

SEBORRHEIC KERATOSIS AND VARIANTS**Variant: Hyperkeratotic Seborrheic Keratosis (Stucco Keratosis)**

Tiny white firm
and rough
hyperkeratotic
lesions



Acanthosis.
Hyperkeratotic
spikes



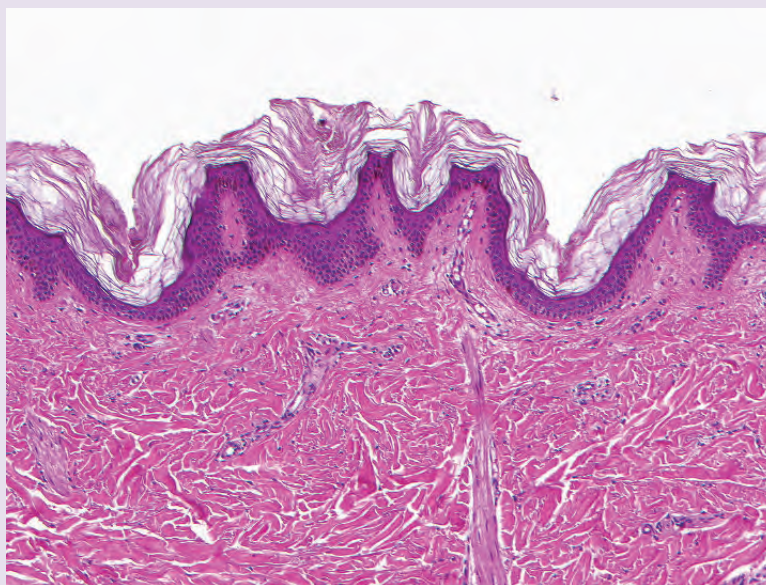
Hi: Acanthosis and orthohyperkeratotic spikes.

Confluent and Reticulate Papillomatosis (Gougerot and Carteaud)

Confluent and reticulated brownish patches resembling pityriasis versicolor



Hyperkeratosis and slight acanthosis; no inflammation



Cl: Gray-brown tiny asymptomatic papules, similar to seborrheic keratosis, coalescing to larger plaques or reticular net, resembling pityriasis versicolor or acanthosis nigricans. Sternum and back are the favorite localisations.

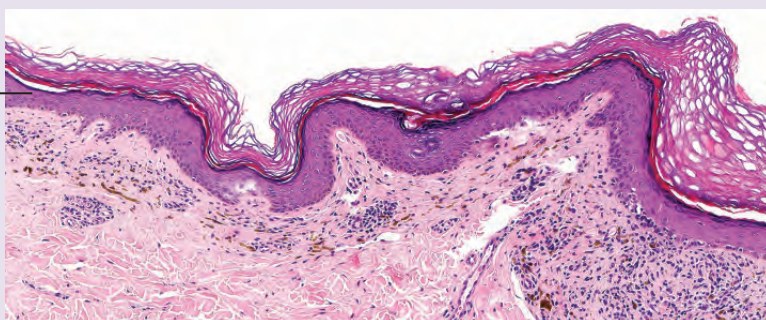
Hi: Slight papillomatosis and hyperkeratosis resembling acanthosis nigricans. Often colonization with *Pityrosporon (Malassezia) orbiculare* (PAS stain).

Reticulate Pigmented Anomaly of the Flexures (Dowling–Degos Disease)

Reticulate hyperpigmentation on the lateral side of the chest



Slight atrophy

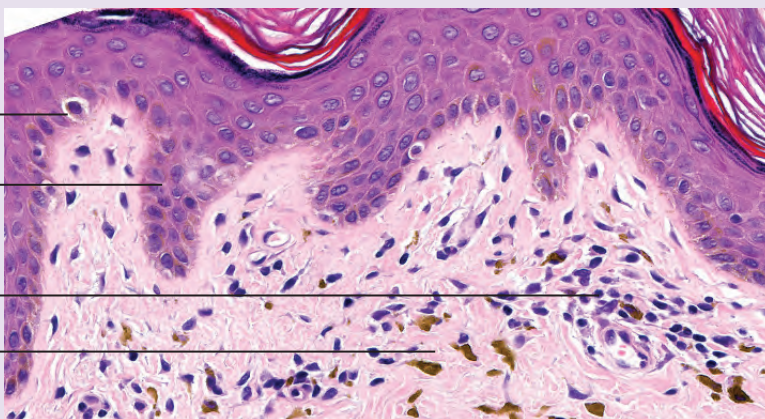


Melanocyte

Downward projection of rete ridges

Slight inflammation

Melanophages loaded with pigment



CI: Congenital, autosomal dominant inherited disease (mutation in the keratin 5-gene *KRT5*), manifesting mostly in adults. Symmetrical small brown macules, resulting in reticular hyperpigmentation of flexural areas (cubital and popliteal fossae, axillae, lateral aspects of the neck, groins).

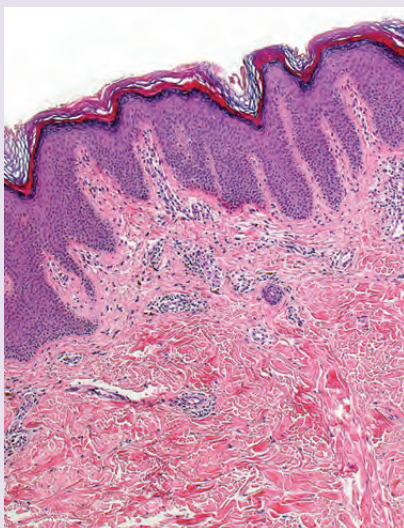
Hi: Similar to flat seborrheic keratosis with basal hyperpigmentation; normal number of melanocytes. Downward projection of the epidermal rete ridges.

Acanthosis Nigricans

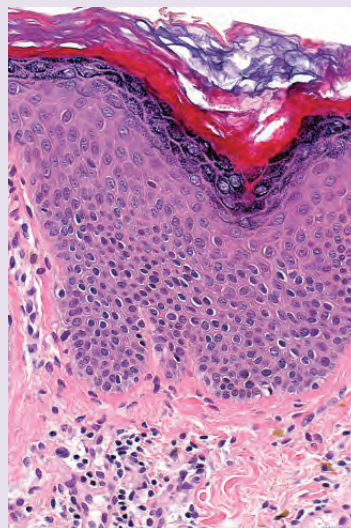
Gray-brown verruciform papules and crests



Alternate ortho- and parahyperkeratosis, acanthosis, papillomatosis (left)



Morphological variant with marked hypergranulosis (right)



Cl: Gray-brown verruciform papules in major intertriginous and flexural areas or neck. The skin shows a velvety surface with crests. It may be associated with a variety of underlying disorders, including obesity (pseudo-acanthosis nigricans benigna), congenital syndromes, hormonal disorders, or malignancies as a paraneoplastic process (acanthosis nigricans maligna).

Hi:

- Alternate ortho- and parahyperkeratosis
- Acanthosis
- Papillomatosis
- Little or no basal layer hyperpigmentation

DD: Acrochordon; small seborrheic keratosis; epidermal nevus.

Solar (Actinic) Keratosis

Multiple solar (actinic) keratoses on the scalp



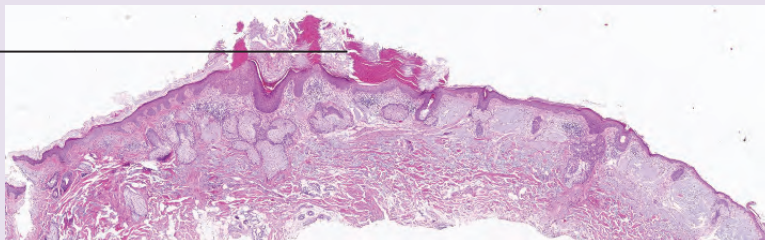
Cl: Actinic keratoses are considered by some to be squamous cell carcinomas *in situ*. However, from a prognostic point of view, they are nosologically different. They are induced by chronic (sunlight) UV exposure and therefore the most common locations are the face, especially nose and ears, and back of the hands and the scalp of bald-headed men. Several variants exist: hypertrophic, bowenoid, atrophic, lichenoid, pigmented. The development of a cutaneous horn, bleeding with hemorrhagic crust, may simulate squamous cell carcinoma or should raise suspicion of malignant transition into squamous cell carcinoma.

Hi:

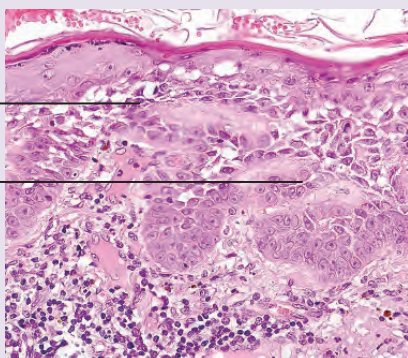
- Many different histological patterns may be seen, reflecting the great clinical variability
- Focal areas of orthohyperkeratosis (pink) alternating with parakeratosis (blue)
- Abnormal keratinocytes, especially in the lower third of the epidermis and the basal layer
- Pseudopod-like proliferations of the epidermis
- In some cases, acantholysis (acantholytic variant) is present in the lower part of the epidermis
- The dysplastic epithelium usually expands downward into the epithelium of the hair follicles
- In the upper dermis, there are solar elastosis and a sparse inflammatory infiltrate and telangiectases

Variant: Acantholytic Solar Keratosis

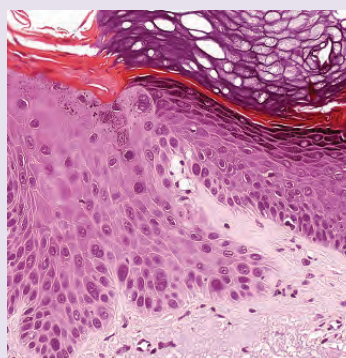
Alternating ortho-
and parakeratosis



Dyscohesive
epidermal pattern.
Suprabasal
acantholysis



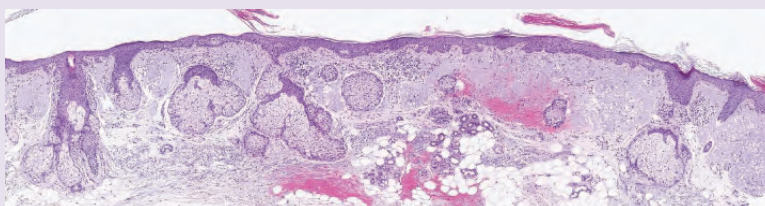
Pseudopod-like
epidermal
projections



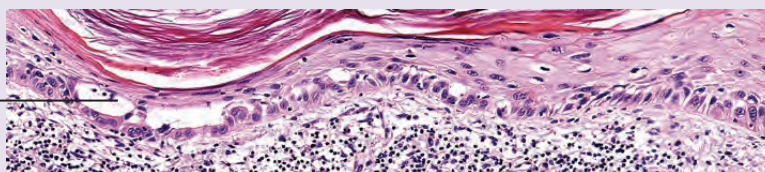
Hi: Suprabasal acantholysis and split formation.

Variant: Atrophic Solar Keratosis

Epidermal
atrophy



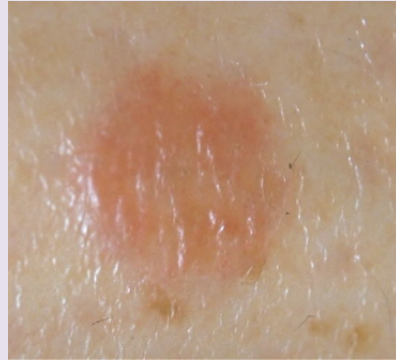
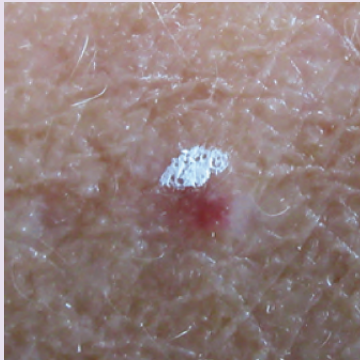
Disruption
of the epidermal
structure.
Suprabasal
splitting
(Freudenthal
lacuna)



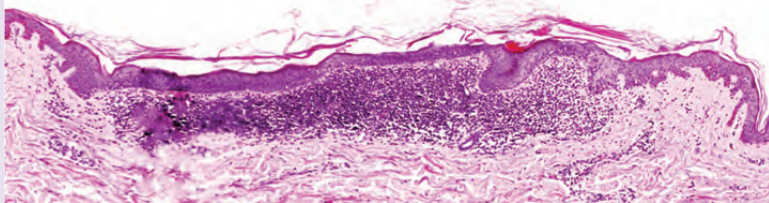
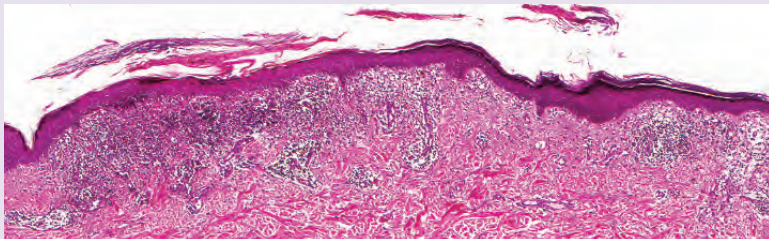
Hi: Atrophy of the epidermis.

Variant: Lichen Planus-Like Solar Keratosis

Lichen planus-like keratoses on the lower arm



Epidermal atrophy. Lichenoid infiltrate in the upper dermis



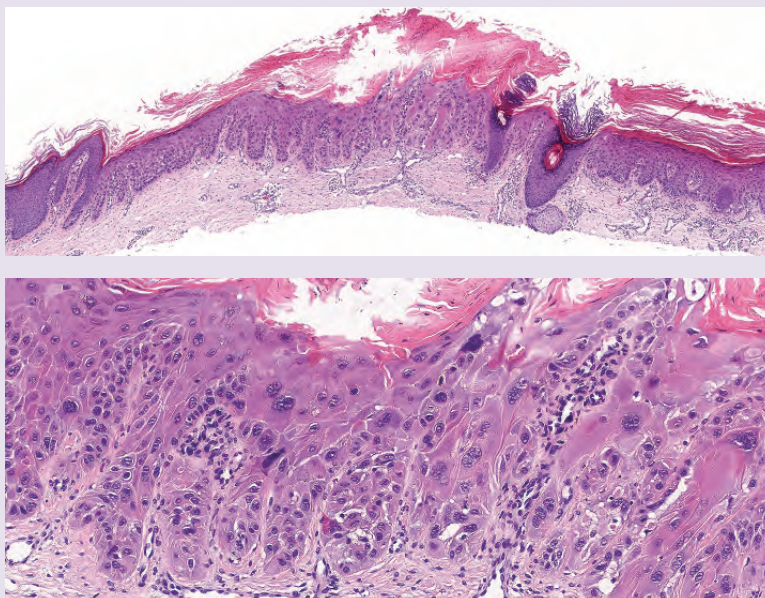
Cl: Circumscribed erythematous plaque, not necessarily hyperkeratotic.

Hi:

- Alternating para- and orthohyperkeratosis
- Acanthosis
- Lichenoid infiltrate in the upper dermis

Variant: Hypertrophic (Bowenoid) Solar Keratosis

Hyperkeratosis, acanthosis, papillomatosis, atypical keratinocytes in all levels of the epidermis featuring a bowenoid pattern



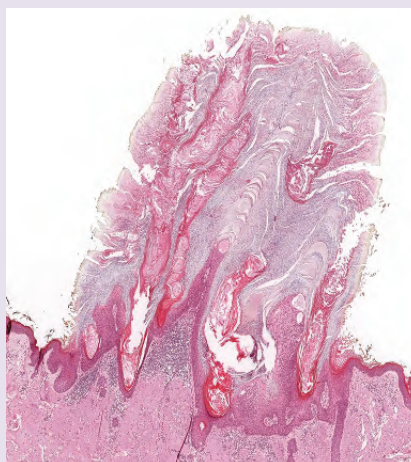
Hi:

- Hypertrophic epidermis
- Bowenoid features with atypical cells in mid and lower levels of the epidermis

Cornu Cutaneum

Keratotic horn on actinic keratoses (left)

Spike-like apposition of horny masses on top of a hypertrophic actinic keratosis (right)



This clinical term describes the apposition of horny material forming a horn. It may be seen in association with various underlying disorders, including actinic keratosis, lupus erythematosus, radiation-induced scars, keratoacanthoma, squamous cell carcinoma, and several other conditions.

Cl: Horn-like hyperkeratosis.

Hi:

- Massive apposition of ortho- or parakeratotic horny masses
- Specific changes of the respective underlying disorder

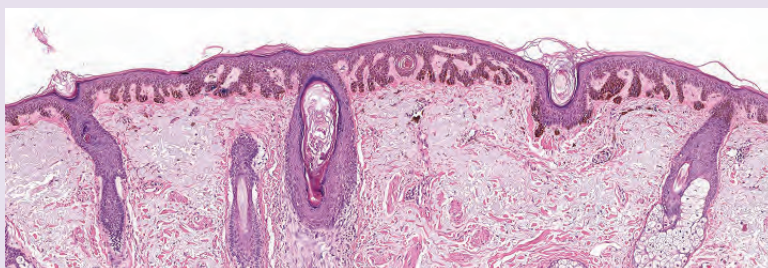
Acanthomas, Non-Viral

Solar Lentigo

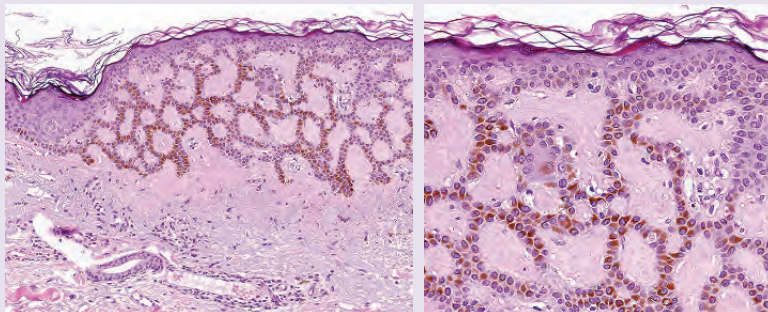


Small bud-like acanthotic proliferations of the epidermis

Actinic elastosis in the dermis



Markedly interconnected hyperpigmented epidermal strands ("dirty feet")



CI: Multiple brown pigmented macules in sun-exposed locations in elderly individuals.

Hi:

- Small, bud-like acanthotic proliferations
- Anastomosing network in some cases
- Hyperpigmentation of the basal layer

- Variable increase of melanocytes
- Solar elastosis in the upper dermis

DD: Pigmented actinic (solar) keratosis and flat seborrheic keratosis.

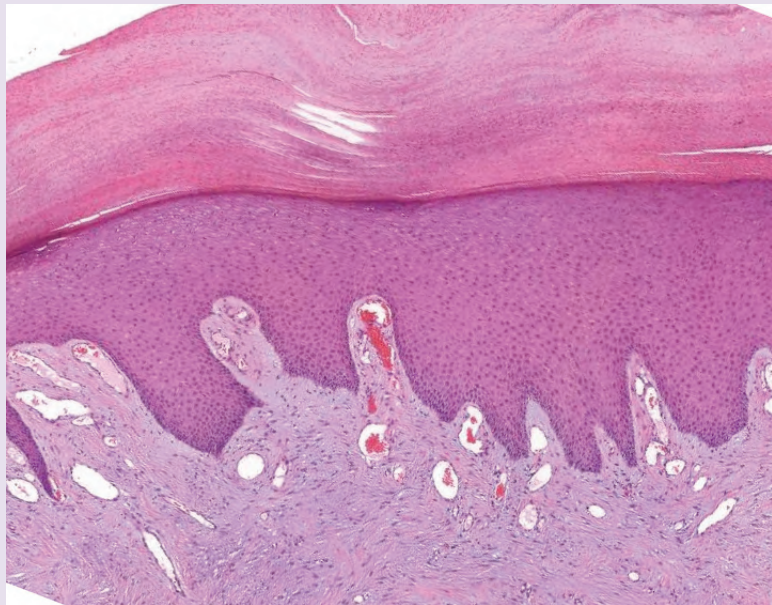
Callus, Factitial Acanthoma

Factitial
acantoma
from chewing



Alternating
stratified
ortho- and
parakeratosis

Marked
acanthosis
with plump
rete ridges



Cl: Corns typically develop in response to pressure and show compact apposition of horny material, sometimes surrounded by faint erythema.

Hi:

- Alternating stratified ortho- and parahyperkeratosis
- Acanthosis of the epidermis without koilocytes

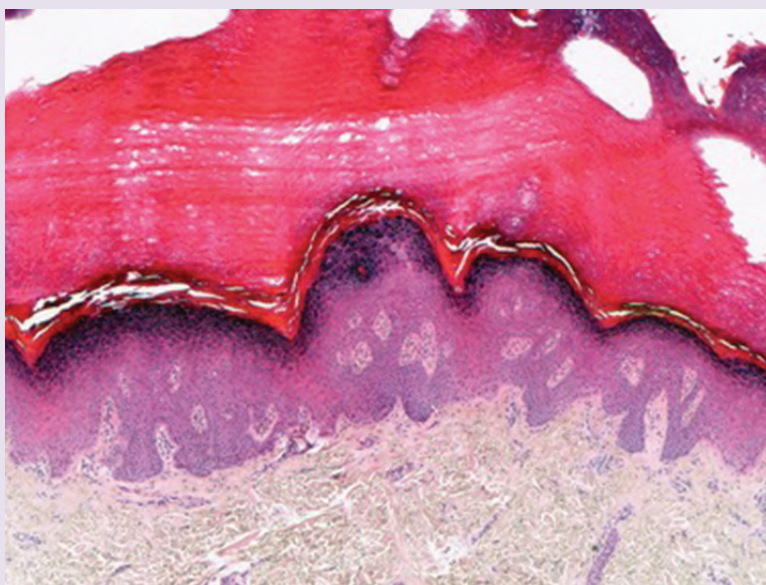
- Pseudopod-like rete ridges
- Granular layer normal or prominent
- Fibrosis and telangiectases

Knuckle Pads (Chewing Pads)

Knuckle pads
in typical
location



Hyperorthokeratosis
with
hypergranulosis
and marked
acanthosis



Cl: Knuckle pads, usually located at the dorsal aspect of the joints of the finger, are considered a subtype of callus.

Hi: See above (callus).

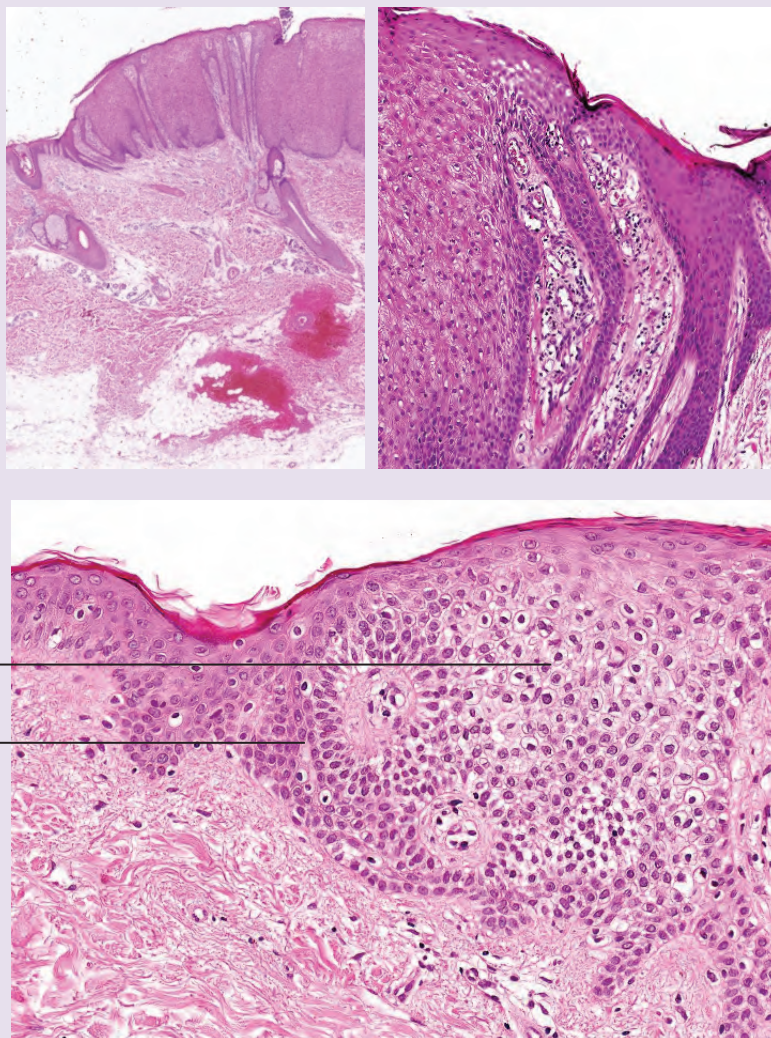
Pale (Clear) Cell Acanthoma

Pale cell
acanthosis
(left)

Psoriasiform
elongation of
rete ridges
(right)

Large
pale cells

Sharp lateral
demarcation



Cl: This uncommon, benign, slowly exophytic growing and slightly hyperkeratotic tumor usually presents as a solitary sharply bordered lesion on the leg of elderly individuals.

Hi:

- Slight hyperkeratosis

- Acanthotic epidermis, dominated by large pale cells which replace all but the basal layer
- Sharp demarcation against the adjacent normal epidermis
- Large cells are rich in glycogen (PAS)
- Psoriasiform elongation of rete ridges

References

- Garcia-Gavin, J., Gonzalez-Vilas, D., Montero, I., Rodriguez-Pazos, L., Pereiro, M.M., and Toribio, J. (2011) Disseminated eruptive clear cell acanthoma with spontaneous regression: further evidence of an inflammatory origin? *Am J Dermatopathol* **33**(6): 599–602.
- Lin, C.Y., Lee, L.Y., and Kuo, T.T. (2016) Malignant clear cell acanthoma: report of a rare case of clear cell acanthoma-like tumor with malignant features. *Am J Dermatopathol* **38**(7): 553–6.
- Shalin, S.C., Rinaldi, C., and Horn, T.D. (2013) Clear cell acanthoma with changes of eccrine syringofibroadenoma: reactive change or clue to etiology? *J Cutan Pathol* **40**(12): 1021–6.

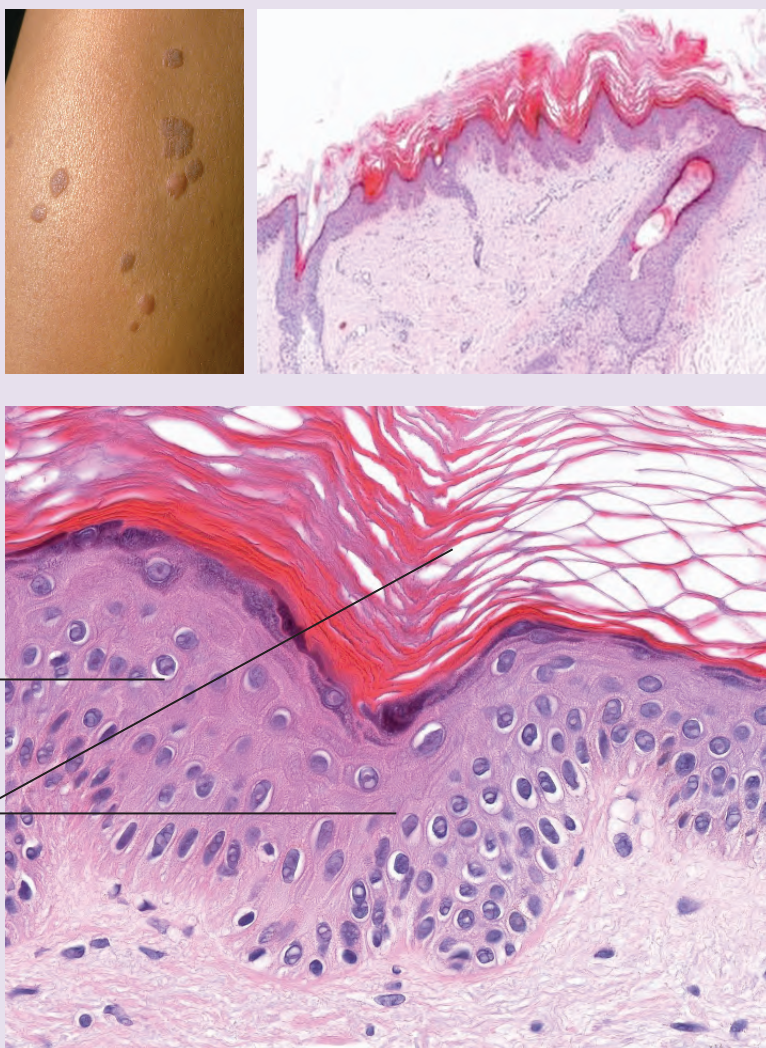
Large Cell Acanthoma

Keratotic lesions
on the left arm

Alternating ortho-
and parakeratosis
(right)

Epidermal cells
twice as large
as normal

Sharp border



Cl: This pale flat benign tumor with sharp borders in sun-exposed areas is considered to be a variant of solar keratosis and is a histological rather than a clinical diagnosis.

Hi:

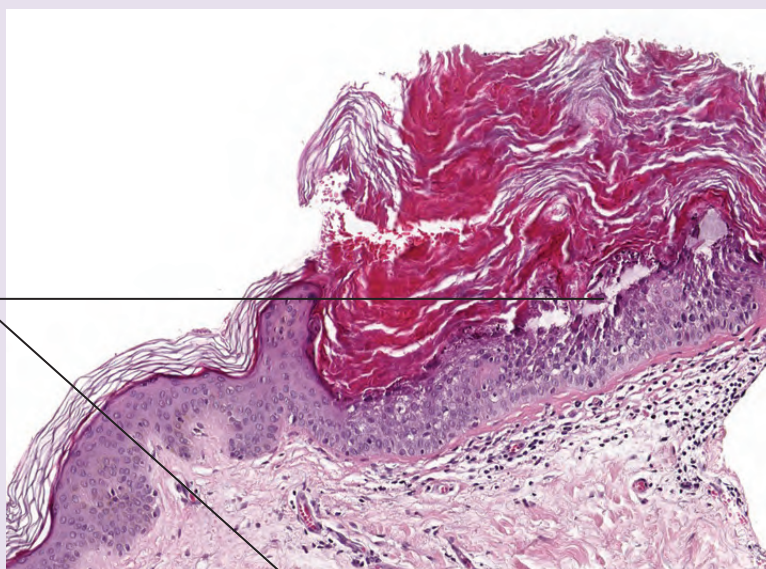
- Hyperkeratosis
- Keratinocytes are twice as large as in normal epidermis
- Sharp demarcation from adjacent normal epidermis

Reference

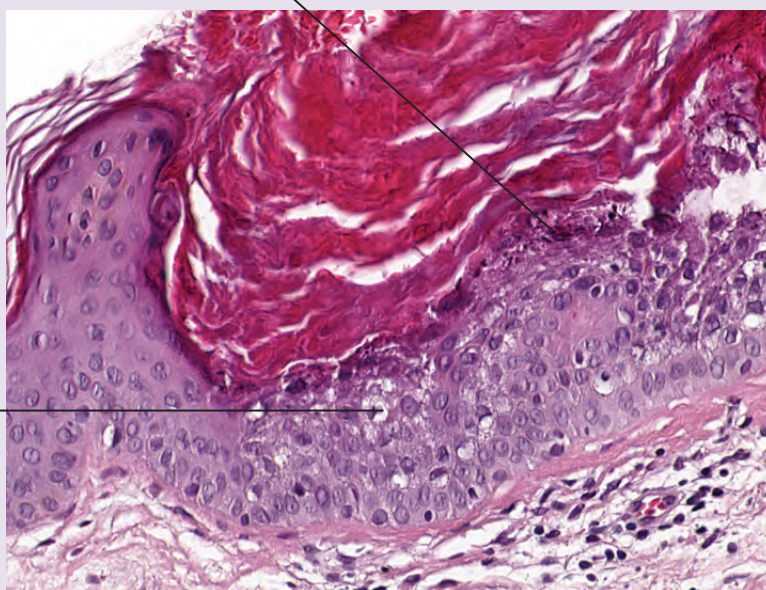
Fraga, G.R., and Amin, S.M. (2014) Large cell acanthoma: a variant of solar lentigo with cellular hypertrophy. *J Cutan Pathol* **41**(9): 733–739.

Differential Diagnosis: Epidermolytic Acanthoma

Hyper- and dyskeratosis



Epidermolytic cells, vacuolisation, keratohyalin granules



Cl: Epidermolytic acanthoma are uncommon solitary or disseminated benign tumors on the trunk or in the anogenital region presenting as wart-like lesions.

Hi:

- Hyper- and dyskeratosis
- Vacuolisation in the spinous and granular layer
- Keratohyaline granules
- Suprabasal epidermolytic cells in the upper two-thirds of the epidermis
- Suprabasilar vesiculation may occur

DD: Epidermolytic hyperkeratosis as seen in congenital ichthyosiform erythroderma, incidental finding in other lesions such as actinic keratosis,

transient acantholytic dermatosis (Grover's), dyskeratosis follicularis (Darier's).

References

- Egozi-Reinman, E., Avitan-Hersh, E., Barzilai, A., Indelman, M., and Bergman, R. (2016) Epidermolytic acanthoma of the genitalia does not show mutations in KRT1 or KRT10. *Am J Dermatopathol* **38**(2): 164–5.
- Kazlouskaya, V., Lambe, J., and Elston, D. (2013) Solitary epidermolytic acanthoma. *J Cutan Pathol* **40**(8): 701–707.

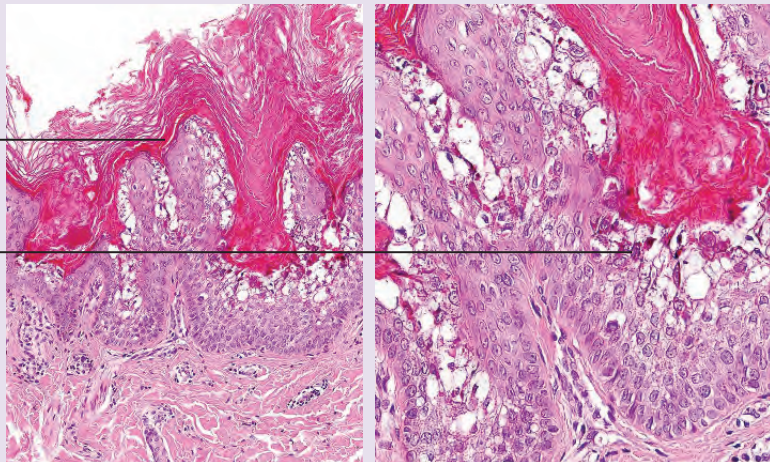
Differential Diagnosis: Congenital Ichthyosiform Erythroderma

Eczema-like skin lesions in a child



Acantholytic keratinocytes

Large keratohyalin granules



Inborn keratinization disorder with widespread skin lesions at birth or early in life.

Cl: Widespread erythroderma with blistering transforming to warty plaques, preferentially located in big flexural skinfolds.

Hi:

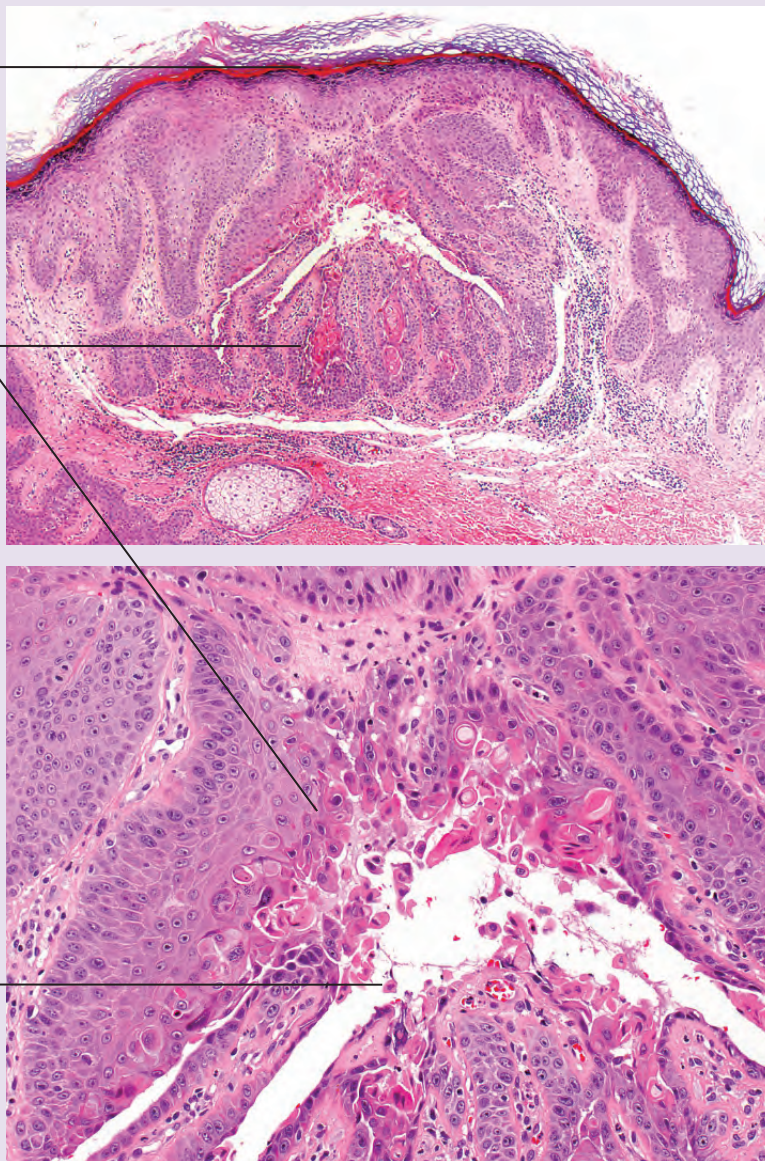
- Thick epidermis
- Acanthokeratolysis
- Clumps of keratin tonofilaments

Acantholytic Acanthoma

Variable stratified ortho- and para-hyperkeratosis

Dyskeratosis

Acantholytic split formation



Cl: Solitary or multiple papules most commonly found on the trunk, anogenital or mucosal areas, resembling verruca vulgaris or seborrheic keratosis. Immunosuppression may be an underlying pathogenetic factor.

Hi:

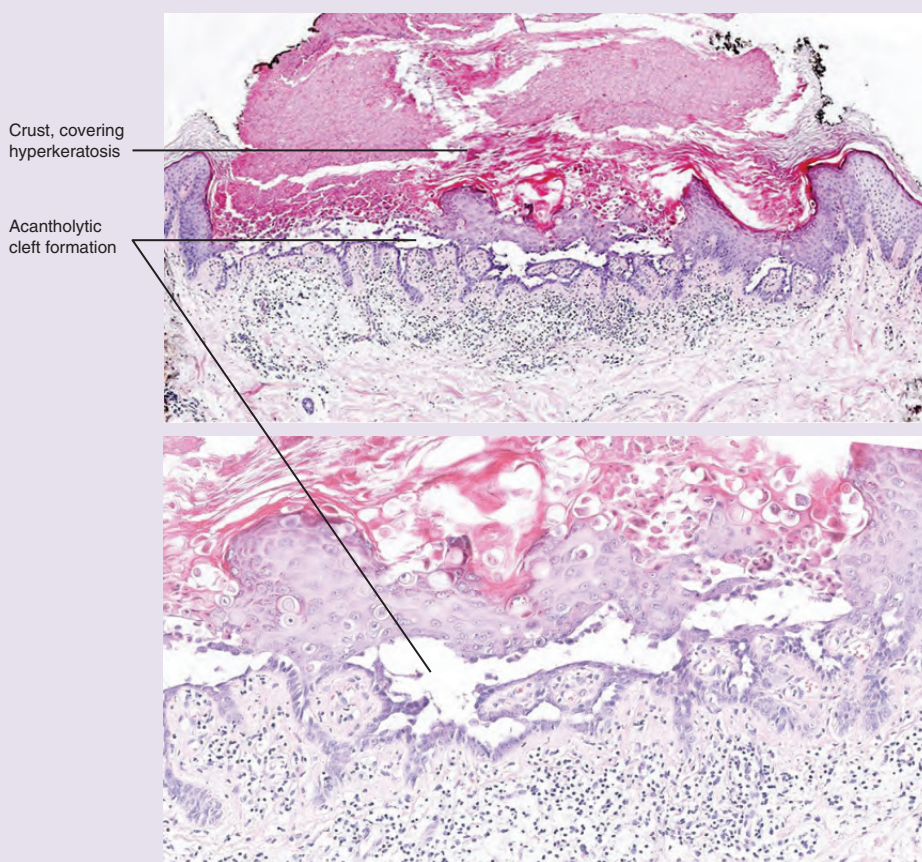
- Variable hyperkeratosis
- Symmetrical, well-circumscribed downward proliferation of keratinocytes without atypia
- Dyskeratosis
- Prominent acantholysis throughout all epidermal layers is the hallmark of the lesions

DD: Resembles Hailey–Hailey, Grover’s or pemphigus, but the process is localized.

References

- Brownstein, M.H. (1988) Acantholytic acanthoma. *J Am Acad Dermatol* **19**(1): 783–6.
- Megahed, M., and Scharffetter-Kochanek, K. (1993) Acantholytic acanthoma. *Am J Dermatopathol* **15**(3): 283–5.

Warty Dyskeratoma



Warty Dyskeratoma

Dyskeratotic
epithelia:
Corps ronds
and grains



Cl: Solitary verrucous papule, sometimes crusted when traumatized.

Hi: Warty dyskeratoma simulates the histological features of Darier's disease and has been considered to be a localized variant of that disease.

- Papular or verrucous lesion
- Focal parakeratosis
- Irregular acanthosis with acantholysis

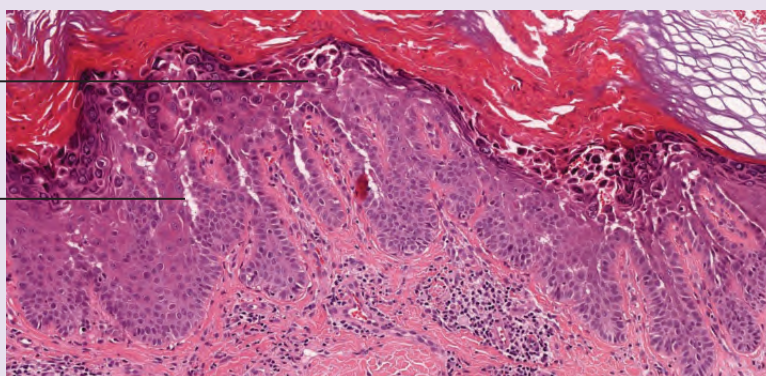
- Dyskeratotic corps ronds and grains
- Frequent association with pilosebaceous structures

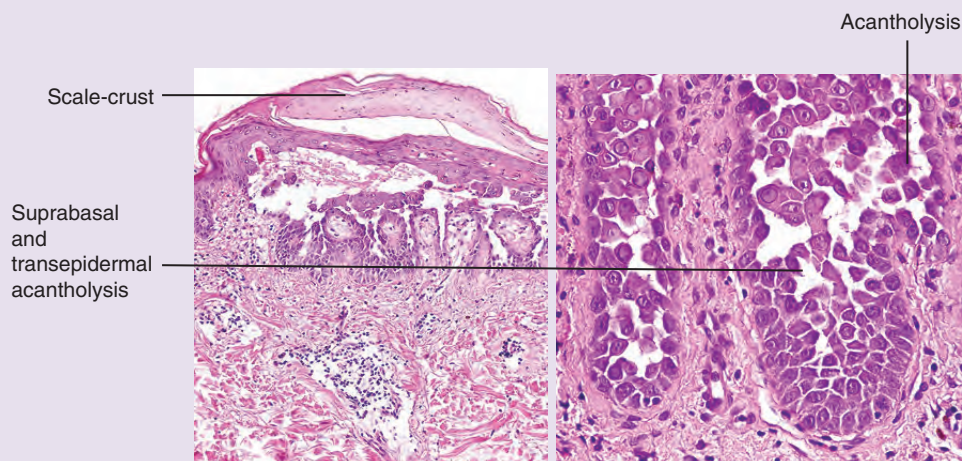
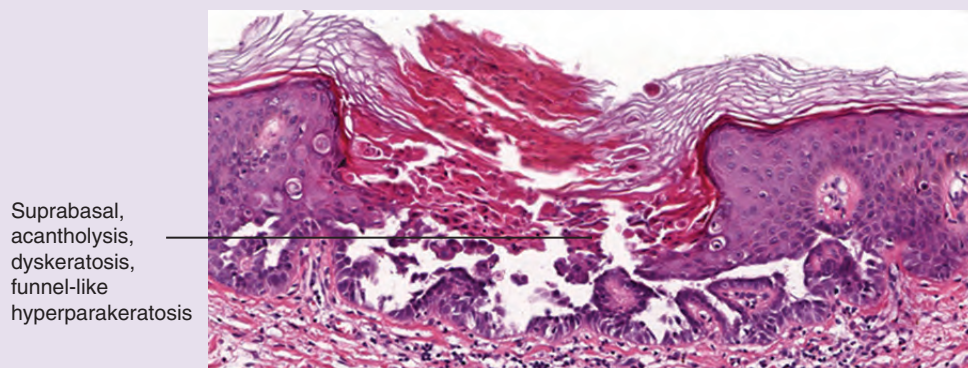
DD: Dyskeratosis follicularis (Darier's disease; see Volume I, page 65), pemphigus benignus familiaris (Hailey–Hailey; see Volume I, page 64), transient acantholytic dermatosis (Grover's disease; see Volume I, page 67).

DD: Dyskeratosis Follicularis (Darier)

Dyskeratosis
with corps ronds
and grains

Suprabasal
acantholysis



DD: Pemphigus Benignus Familiaris (Hailey-Hailey)**DD: Transient Acantholytic Dermatitis (Grover's Disease)****References**

- Lora, V., Scarabello, A., and Cota, C. (2015) Warty dyskeratoma as a cutaneous horn of the mons pubis. *Am J Dermatopathol* **37**(10): 802–4.
- Martorell-Calatayud, A., Sanmartin-Jimenez, O., Traves, V., and Guillen, C. (2012) Numerous umbilicated papules on the trunk: multiple warty dyskeratoma. *Am J Dermatopathol* **34**(6): 674–5.

Porokeratoma (Porokeratosis Mibelli)

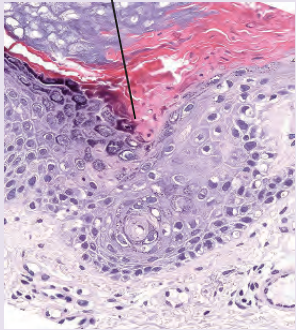
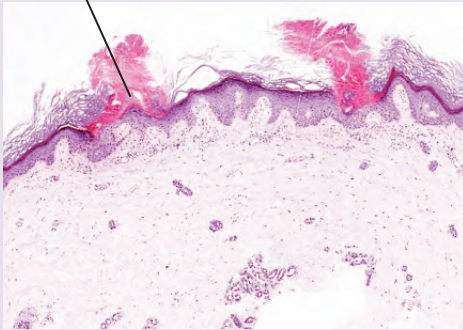
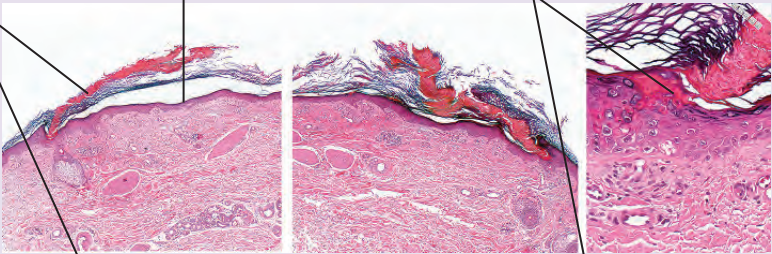
Slightly atrophic
patches with
hyperkeratotic
borders



Cornoid lamellae
on opposite
sides

Atrophy of the epidermis

Para- and dyskeratosis



This group of autosomal dominant inherited keratinization disorders is defined histologically by the presence of a cornoid lamella, which is seen best when the biopsy is taken perpendicular to the border of the lesion.

Cl: The lesions may appear at any age and occur more often in men. The extremities are the favored sites of manifestation, but other parts of the body may also be affected. The initial lesion starts as a small red papule with a central keratotic spine which spreads peripherally, forming a slightly atrophic patch with irregular hyperkeratotic borders. Linear porokeratosis and giant porokeratosis are variants. There is an increased risk for the development of squamous cell carcinoma.

Hi:

- No relationship to sweat pores, as suggested by the name
- Narrow ridge of hyperkeratosis with parakeratosis (cornoid lamella)
- Cornoid lamella (with PAS-positive grains) amidst parakeratotically layered corneocytes
- Dyskeratotic cells are almost always found beneath the cornoid lamella
- Focal absence of stratum granulosum
- Central atrophy of the epidermis – imitating atrophic lupus erythematosus
- Underlying lichenoid infiltrate
- Advanced stages may show epithelial dysplasia in the center

References

- Biswas, A. (2015) Cornoid lamellation revisited: apropos of porokeratosis with emphasis on unusual clinicopathological variants. *Am J Dermatopathol* **37**(2): 145–55.
- Tallon, B., and Emanuel, P. (2017) Follicular porokeratosis, a porokeratosis variant. *Am J Dermatopathol* **39**: e1-7–e109.
- Tan, T.S., and Tallon, B. (2016) Pigmented porokeratosis. A further variant? *Am J Dermatopathol* **38**(3): 218–21.

Acanthomas, Viral

Verruca Vulgaris

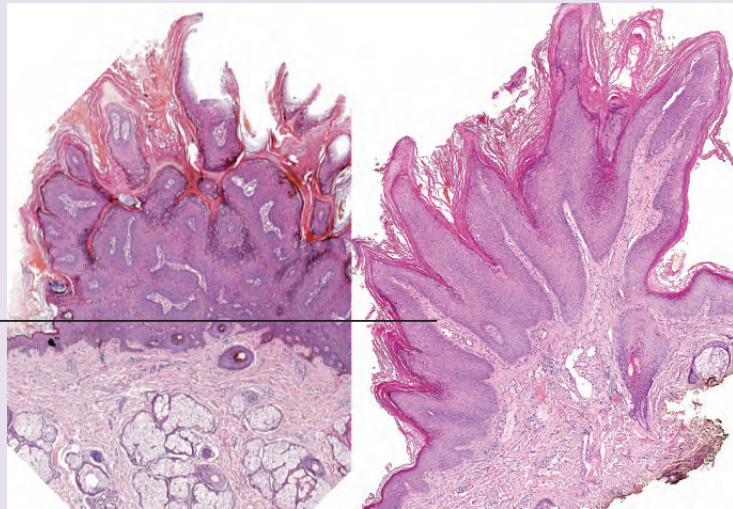
Hyperkeratotic verrucae on fingers and nose



Verruca Vulgaris

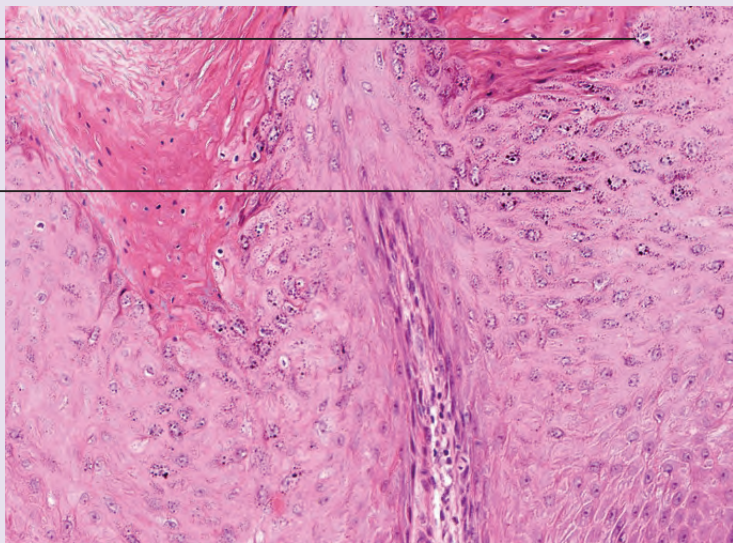
Digitated
epidermal
hyperplasia

Papillomatosis
with
dilated vessels

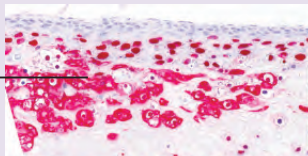


Koilocytes

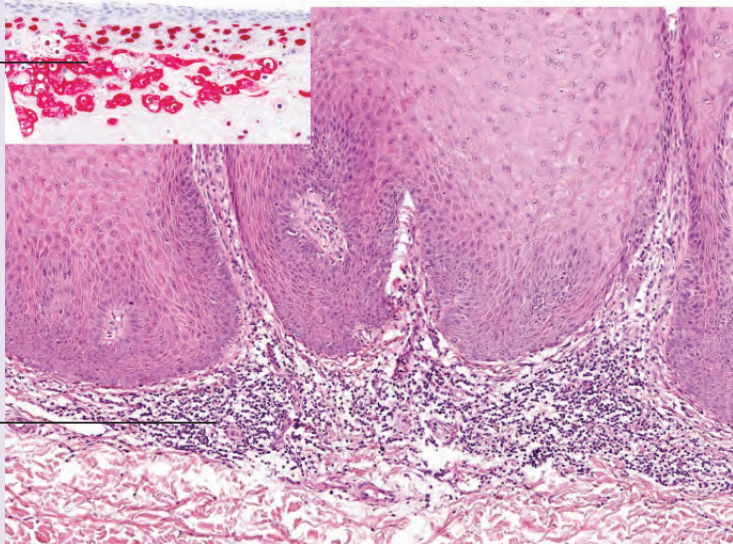
Hypergranulosis



Anti HPV
antibody-labelling



Inflammatory
infiltrate



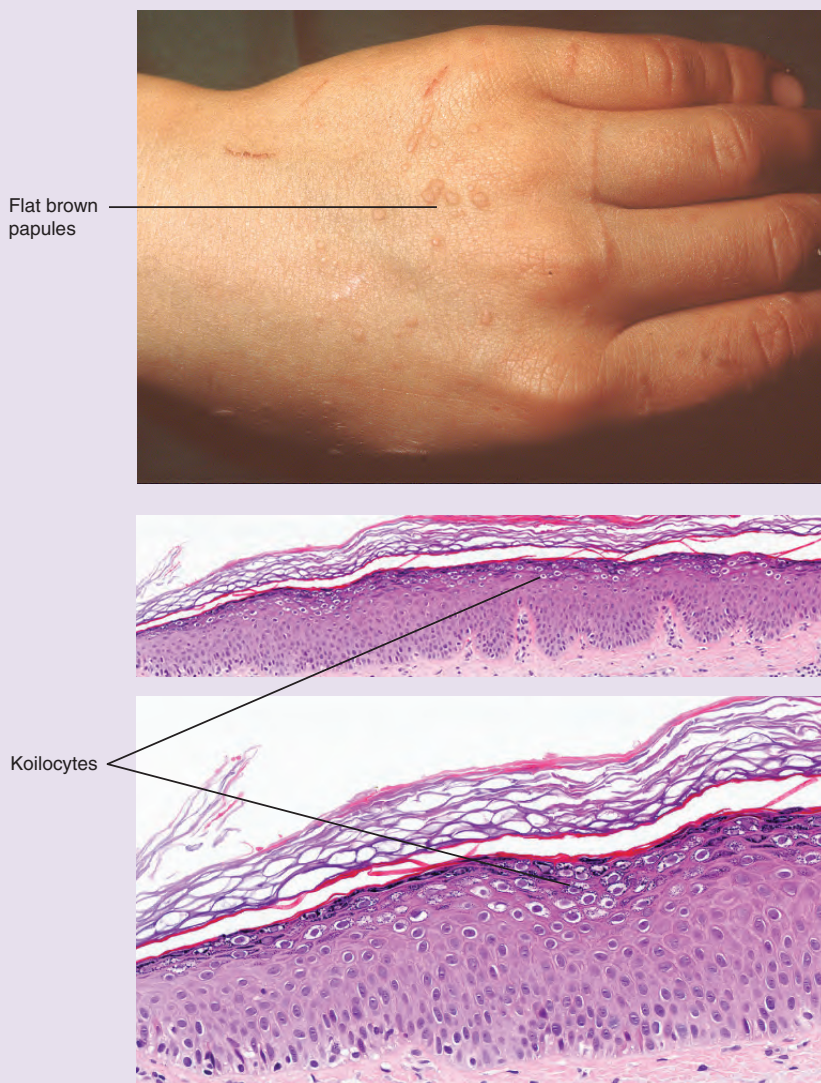
HUMAN PAPILLOMA VIRUS (HPV)

Cl: Solitary or grouped papules showing massive hyperkeratosis and sometimes significant inflammation.

Hi:

- Epidermal hyperplasia with a “multiple raised fingers” silhouette
- Hyperkeratosis with focal parakeratosis
- Intracorneal inclusions of hemorrhagic exudate (capillary thrombi)
- Hypergranulosis with enlarged keratohyalin granules
- Koilocytes (bird’s eye cells) in the granular layer and upper stratum spinosum
- Dilated vessels in the papillary dermis
- Inflammatory infiltrate in the upper dermis

Variant: Verruca Plana



HUMAN PAPILLOMA VIRUS (HPV)

Cl: Flat hyperkeratotic (verruciform) papules.

Hi:

- Hyperkeratosis
- Slight acanthosis
- No papillomatosis
- Confluent band of koilocytes (bird's eye cells) in the granular layer

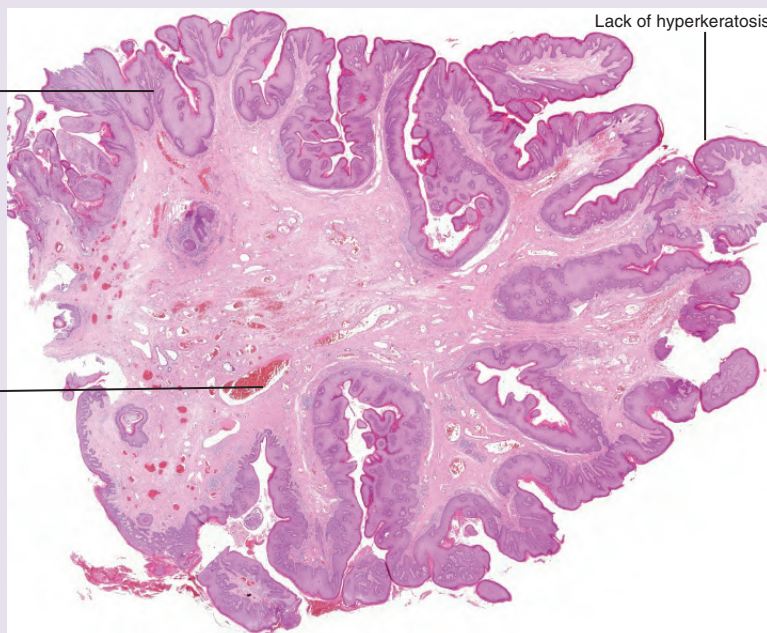
Variant: Condyloma Acuminatum

Cauliflower-like proliferations



Acanthosis, papillomatosis,

Dilated vessels



Cl: Papular and verruciform lesions in anogenital or oral localisation.

Hi: Acanthopapilloma with focal hyperparakeratosis and lack of pseudocysts (“naked seborrheic

keratosis”). Presence of koilocytes, even sometimes sparse.

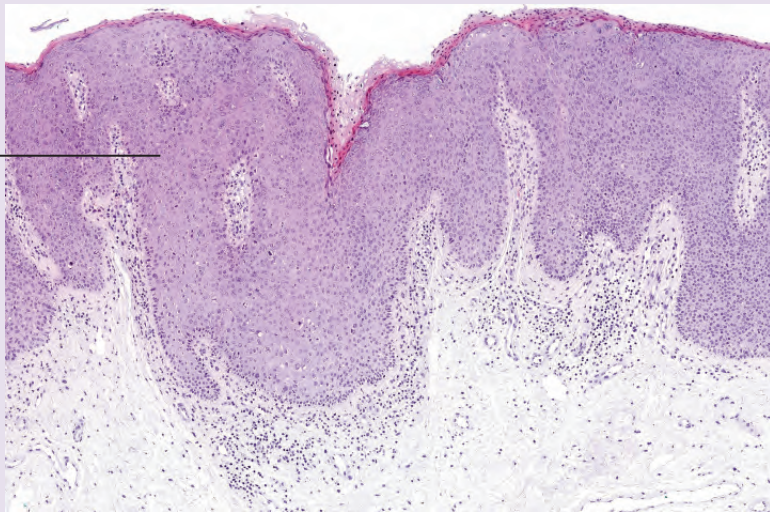
HUMAN PAPILLOMA VIRUS (HPV)

Bowenoid Papulosis

Flat papules

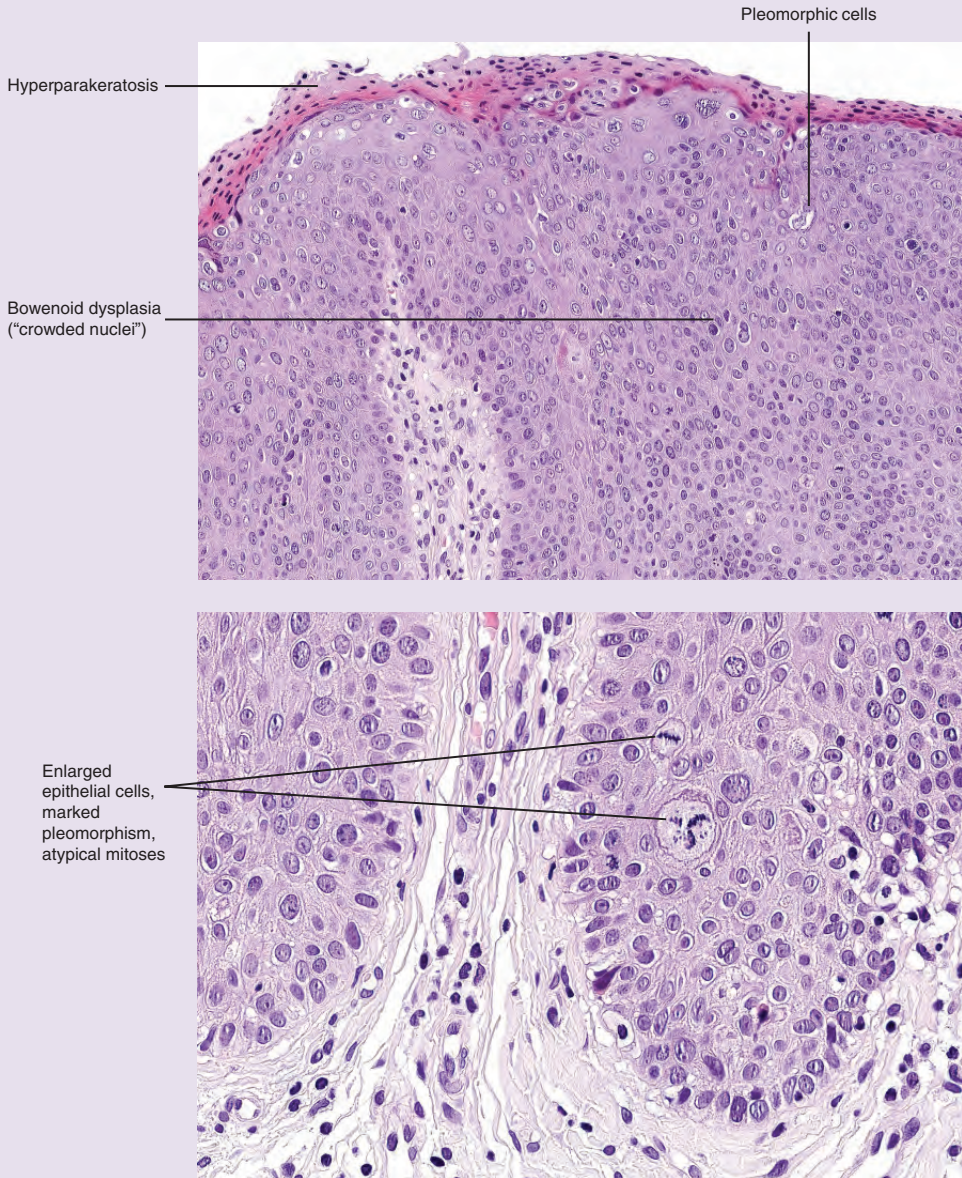


Acanthosis,
papillomatosis,
marked dysplasia



HUMAN PAPILLOMA VIRUS (HPV)

Bowenoid Papulosis



Cl: Solitary or confluent flat papular eruptions in anogenital localisation, often associated with oncogenic HPV infection (HPV16, HPV18).

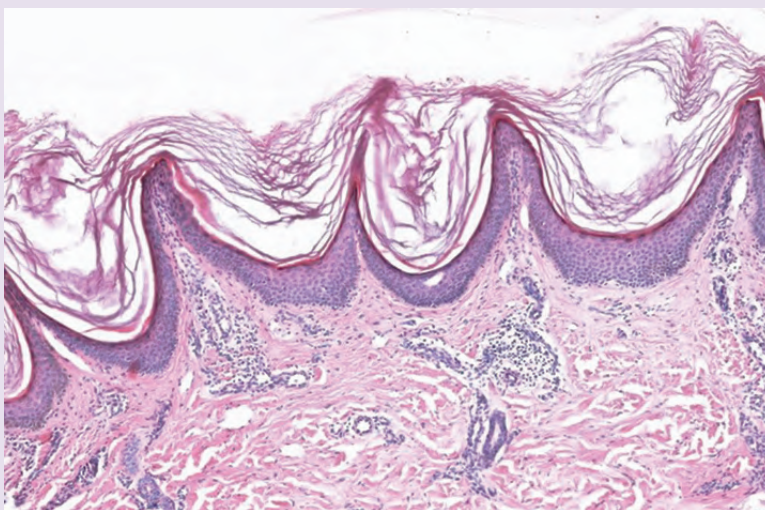
Hi: Atypical epithelial cells with nuclear pleomorphism and mitotic activity, identical with Bowen's disease.

HUMAN PAPILLOMA VIRUS (HPV)**Acrokeratosis Verruciformis (Hopf)**

Flat hyperkeratotic papules on the dorsum of the hand



Hyperkeratosis, wavy acanthosis, papillomatosis



Considered to be associated with HIV infection by some and to be an autosomal dominant inherited disorder by others. There is close relationship to Darier's disease and to epidermodysplasia verruciformis.

Cl: Multiple flat hyperkeratotic papules in distal parts of the extremities (dorsa of the hands, feet, forearms).

Hi:

- Orthohyperkeratosis
- Wavy acanthosis
- Papillomatosis
- Thin papillae

MOLLUSCUM POXVIRUS

References

Bergman, R., Sezin, T., Indelman, M., Helou, W.A., and Avitan-Hersh, E. (2012) Acrokeratosis verruciformis of Hopf showing P602L mutation in ATP2A2 and overlapping histopathological features with Darier disease. *Am J Dermatopathol* **34**(6): 597–601.

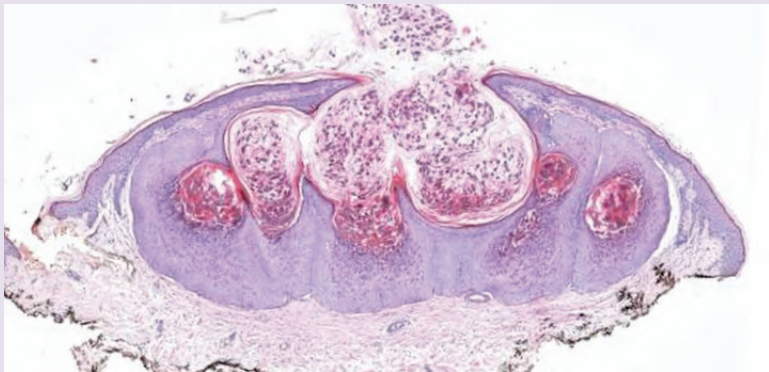
Matsumoto, A., Gregory, N., Rady, P.L., Tyring, S.K., and Carlson, J.A. (2017) Brief Report: HPV-17 infection in Darier disease with acrokeratosis verrucosus of Hopf. *Am J Dermatopathol* **39**(5): 370–3.

Molluscum Contagiosum

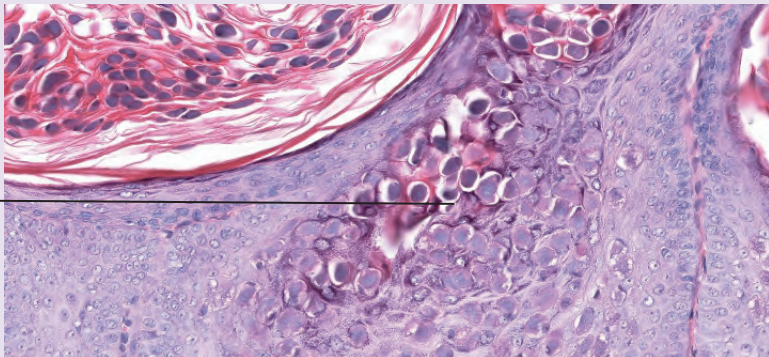
Grouped
umbilicated
papules



Crateriform
symmetric tumor
with Molluscum
bodies



Molluscum
bodies
(basophilic
virus capsid –
Molluscum
poxvirus)



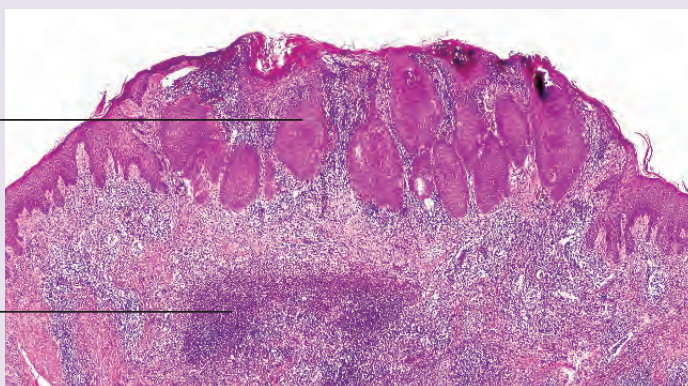
MOLLUSCUM POXVIRUS

Cl: Molluscum poxvirus is the causative agent. Typically children and immunocompromised patients are affected. Lesions are mostly multiple, sometimes extensive and eczematous. Characteristic features are elevated papules with a central dell.

Hi:

- Epidermal hyperplasia
- Central invagination, corresponding to the clinically visible dell
- Dell filled with necrotic keratinocytes, containing large, prominent, basophilic intracytoplasmic inclusions (molluscum bodies) that stain positive with Melan A
- Massive inflammatory reaction when ruptured

Molluscum Contagiosum, Inflamed



Verrucous hyperplasia. Molluscum bodies faintly visible.

Dense round cell infiltrate – may contain large lymphocytes

Reference

Ishikawa, M.K., Arps, D.P., Chow, C., Hocker, T.L., and Fullen, D.R. (2015) Histopathological features of molluscum contagiosum other than molluscum bodies. *Histopathology* **67**(6): 836–42.

"Pseudocarcinomas" and Neoplasms with Intermediate Malignant Potential

Keratoacanthoma, epithelioma cuniculatum, papillomatosis cutis carcinoides, Buschke–Löwenstein

giant condyloma, and florid oral papillomatosis form a group of disorders which are biologically benign, do not metastasize and histologically simulate large warts or well-differentiated squamous cell carcinoma.

Keratoacanthoma (KA)

Hyperkeratotic crateriform tumor on the nose (left)

Nodule with central keratotic horn (right)



CI: Most KAs develop in sun-exposed areas. They are biologically benign and develop within weeks, in contrast to squamous cell carcinoma which develops over months. Multiple KAs are encountered in conjunction with hereditary cancer syndromes (Muir–Torre) or as specific clinical

variants (e.g. Grzybowski, Ferguson–Smith). The typical lesion is a dome-shaped keratotic nodule with a central dell filled by a keratotic plug. KA centrifugum marginatum is a centrifugal spreading variant, which most commonly occurs on the extremities.

Variant: Keratoacanthoma Centrifugum Marginatum

Centrifugally growing flat hyperkeratotic tumors on hand (left) and lower limb (right)



Variants of Keratoacanthoma

Verrucous carcinoma
(epithelioma cuniculatum)



Papillomatosis cutis carcinoides
(pseudocarcinomatous hyperplasia)



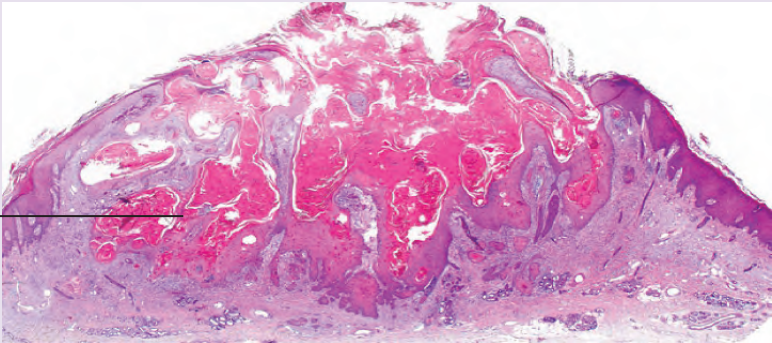
Florid oral papillomatosis



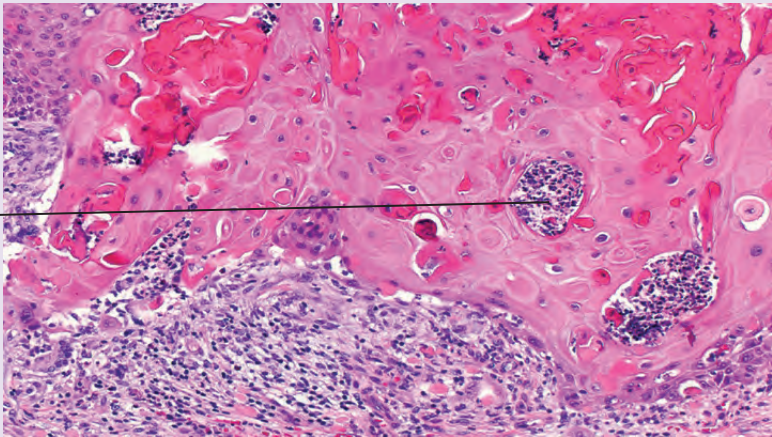
Giant condyloma
(Buschke-Löwenstein)

Keratoacanthoma

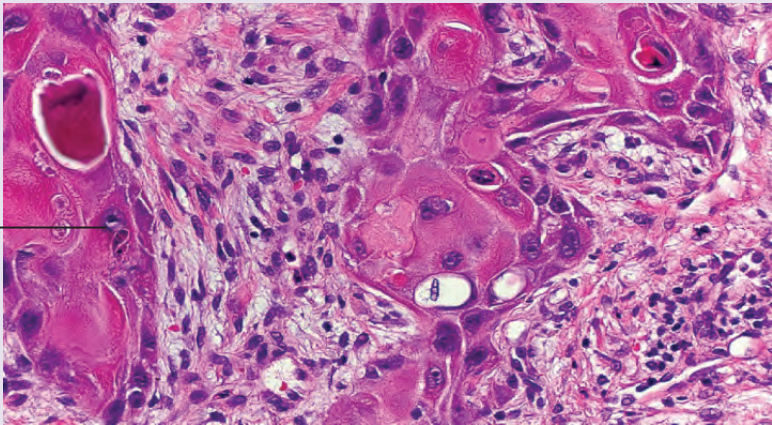
Crateriform
tumor
with central
hyperkeratotic
plugging



Intralesional
microabscesses

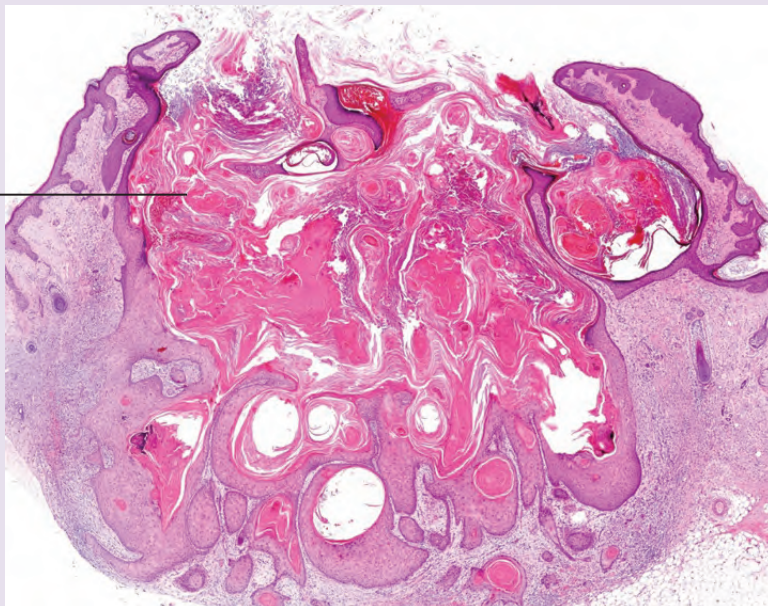


Atypical
keratinocytes



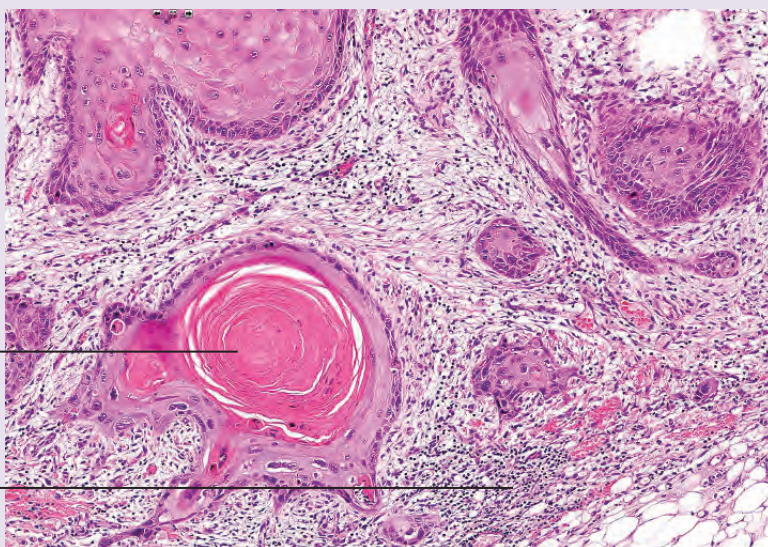
Keratoacanthoma

Central keratotic
plug



Keratotic
plug

Mixed cellular
inflammatory
infiltrate



Hi:

- Symmetrical cup-shaped tumor, filled with cornified debris and with smooth outer margins
- Central keratotic plug with massive acanthosis and papillomatosis
- Bilateral epithelial lip formation of adjacent rete ridges
- Proliferation of atypical keratinocytes and mitoses
- Parakeratosis

- Intraepidermal formation of microabscesses, filled with mixed inflammatory cells and debris
- Mixed cellular infiltrate in the dermis

References

Kluger, N. (2010) Issues with keratoacanthoma, pseudoepitheliomatous hyperplasia and squamous cell carcinoma within tattoos: a clinical point of view. *J Cutan Pathol* **37**(7): 812–13.

Misago, N., Takai, T., Toda, S., and Narisawa, Y. (2014) The histopathologic changes in keratoacanthoma depend on its stage. *J Cutan Pathol* **41**(7): 617–19.

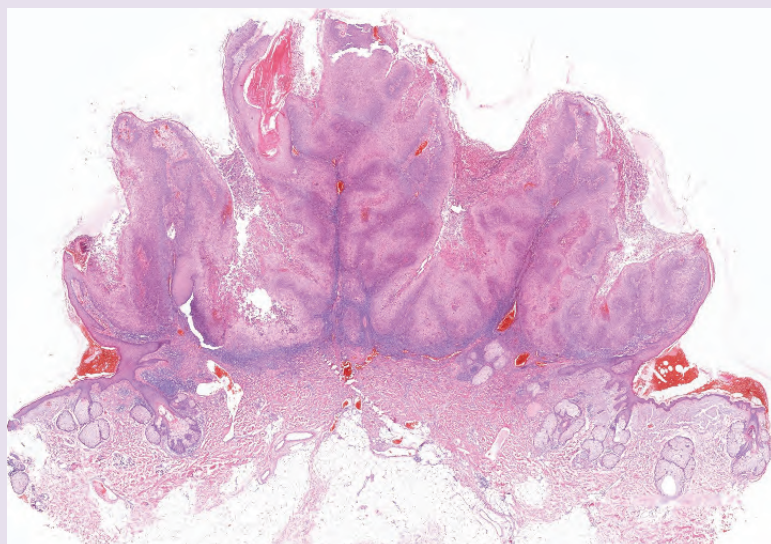
Resnik, K.S. and Kutzner, H. (2010) Of lymphocytes and cutaneous epithelium: keratoacanthomatous hyperplasia in CD30+ lymphoproliferative disorders and

CD30+ cells associated with keratoacanthoma. *Am J Dermatopathol* **32**(3): 314–15.

Savage, J.A. and Maize, J.C. Sr (2014) Keratoacanthoma clinical behavior: a systematic review. *Am J Dermatopathol* **36**(5): 422–9.

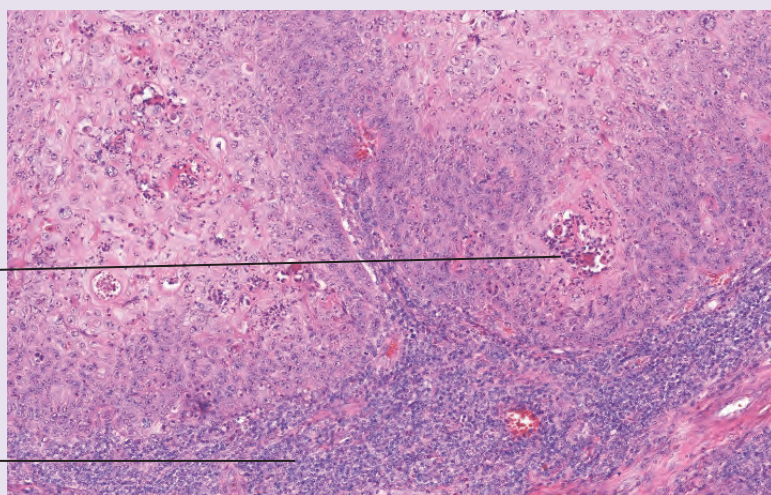
Epithelioma Cuniculatum (Verrucous Carcinoma) (EC/VC)

Exophytic lesion, showing verruciform acanthosis and papillomatosis



Cysts and sinuses, filled with cellular and keratotic debris

Mixed cellular inflammatory infiltrate



Cl: Both exo- and endophytic verrucous lesions, mostly of the soles or perigenital area. Association with HPV infection has been reported.

Hi:

- Exo- or endophytic verrucous hyperkeratosis
- Irregular papillomatosis and acanthosis
- Adjacent epidermis normal
- Well-differentiated keratinocytes
- Low proliferative activity, minimal epithelial dysplasia
- Cysts and sinuses (“fox’s burrow”-like), allowing discharge of pus, blood, or cornified debris

DD: Large warts; well-differentiated squamous cell carcinoma.

Comment: Epithelioma cuniculatum/verrucous carcinoma is a genuine carcinoma, albeit lacking the classic histopathological squamous cell carcinoma features, e.g. massive epithelial dysplasia and high proliferative activity. EC/VC is a unique carcinomatous tumor growing by lack of apoptosis rather than by increased proliferation rate. Pathologists should be aware that behind the silhouette of an exo-endophytic epithelial hyperplasia with minimal cytological atypia and scant mitoses, there is a genuine carcinoma.

References

Kubik, M.J. and Rhatigan, R.M. (2012) Carcinoma cuniculatum: not a verrucous carcinoma. *J Cutan Pathol* **39**(12): 1083–7.

Nakamura, Y., Kashiwagi, K., Nakamura, A., and Muto, M. (2015) Verrucous carcinoma of the foot diagnosed using p53 and Ki-67 immunostaining in a patient with diabetic neuropathy. *Am J Dermatopathol* **37**(3): 257–9.

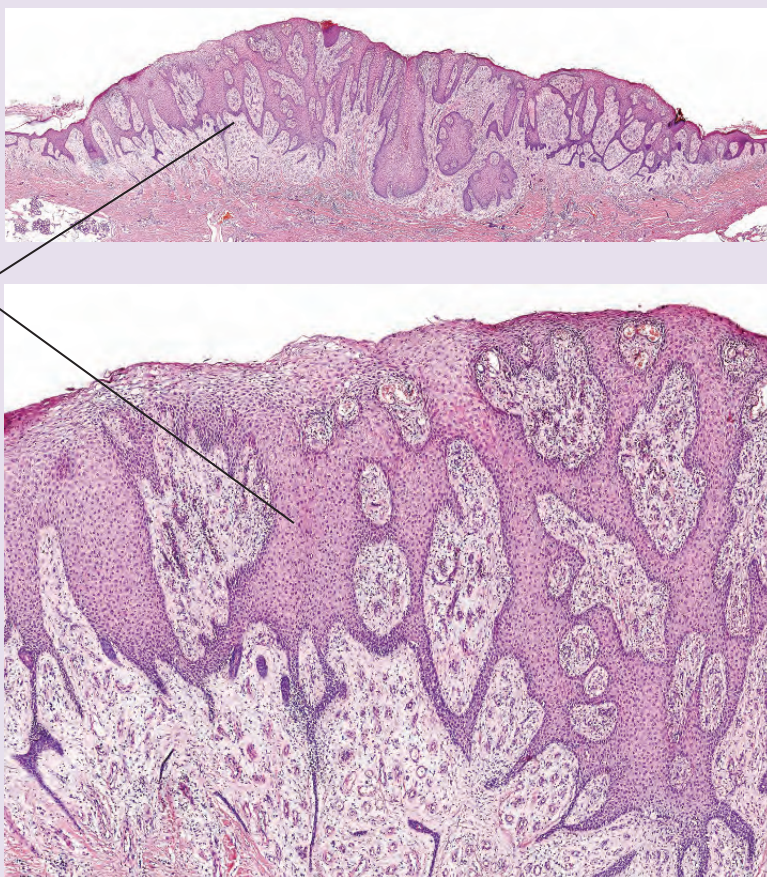
Odar, K., Bostjancic, E., Gale, N., Glavac, D., and Zidar, N. (2012) Differential expression of microRNAs miR-21, miR-31, miR-203, miR-125a-5p and miR-125b and proteins PTEN and p63 in verrucous carcinoma of the head and neck. *Histopathology* **61**(2): 257–65.

Zidar, N., Langner, C., Odar, K., et al. (2017) Anal verrucous carcinoma is not related to infection with human papillomaviruses and should be distinguished from giant condyloma (Buschke–Lowenstein tumour). *Histopathology* **70**(6): 938–45.

Papillomatosis Cutis Carcinoides

Irregular
acanthosis and
papillomatosis

Dermal edema
and fibrosis



CI: Large, cauliflower-like reactive hyperkeratotic process around chronic inflammatory processes, ulceration or tumor, preferentially on the shins or dorsal aspect of the feet, resembling squamous cell carcinoma.

Hi:

- Irregular acanthosis of pale epithelium with elongation of rete ridges
- Irregular papillomatosis
- Normal keratinocytes
- Edema and fibrosis in the upper dermis
- Variable chronic inflammatory changes of the surrounding tissue

DD: Blastomycosis-like pyoderma.

References

- Allerga, F., Manfredi, G., Colli, V., Magnanini, M., and Manfredi, M. (1975) [An uncommon pseudo tumoral skin disease; the so-called Papillomatosis cutis carcinoides. A review (author's transl)]. *Ateneo Parmense Acta Biomed* **46**(6): 649–63.
- Balda, B.R. and Wilhelm, K. (1970) [Verruca vulgaris gigantea with the aspect of papillomatosis cutis carcinoides]. *Hautarzt* **21**(12): 550–2.
- Baldauf, K., Strohbach, F., and Laslop, M. (1982) [Malignant transformation of papillomatosis cutis carcinoides Cottron]. *Z Arztl Fortbild (Jena)* **76**(1–2): 69–71.
- Bues, M., Muller, K.M., and Schwering, H. (1983) [Pseudocancer of the skin following lower leg amputation. Rare case of Gottron's papillomatosis cutis carcinoides]. *Zentralbl Chir* **108**(14): 895–9.
- Cajkovic, V., Trbuljak, M., and Petricic, B. (1970) [Papillomatosis cutis carcinoides Gottron]. *Rad Med Fak Zagrebu* **18**(1): 81–7.
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- Ruppe, J.P. Jr (1981) Verrucous carcinoma. Papillomatosis cutis carcinoides. *Arch Dermatol* **117**(3): 184–5.
- Stevanovic, D.V. (1963) Papillomatosis cutis carcinoides (Gottron). *Oncologia* **16**: 116–22.
- Vilanova, X. and Cabre, J. (1964) [Pseudoepithelioma (J. De Az'ua) Papillomatosis Cutis Carcinoides (Grottron)]. *Actas Dermosifiliogr* **55**: 753–62.

Florid Papillomatosis of the Oral Cavity (Oral Verrucous Carcinoma)

CI: Whitish cobblestone-like plaques and papules of the buccal mucosa. Lesions may progress to cauliflower-like exophytic neoplasms.

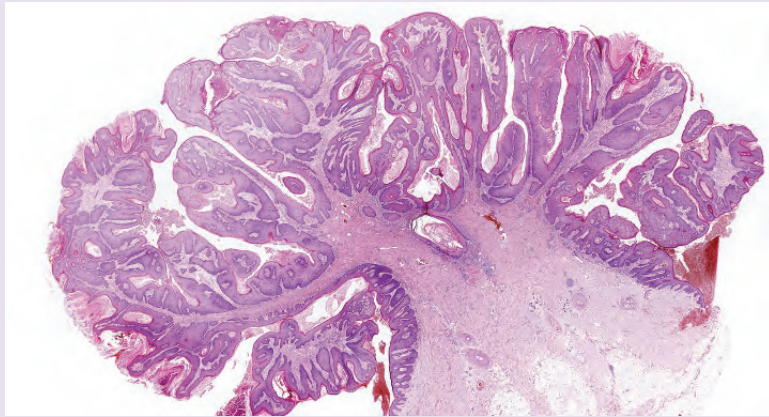
Hi:

- Hyperplastic epithelial layer
- Focal granulositis and slight parakeratosis
- No significant proliferative activity

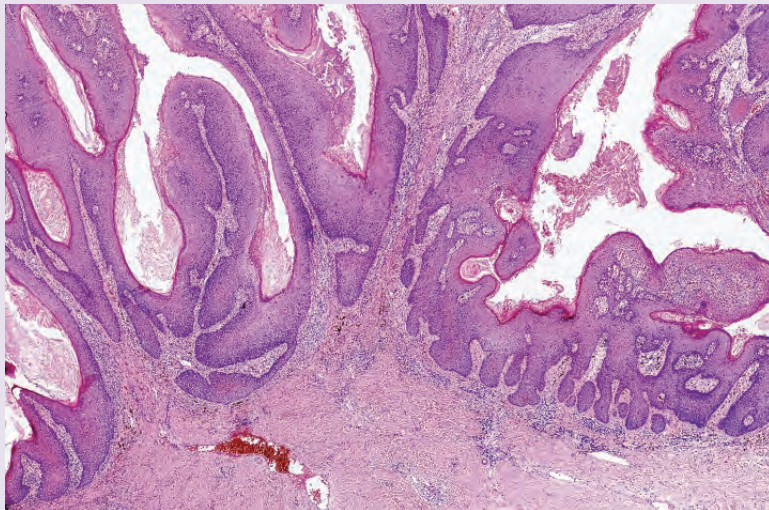
DD: Hairy leukoplakia occurs mostly in immunocompromised patients, preferentially at the lateral margins of the tongue, presenting with poorly circumscribed whitish plaques similar to hyperplastic leukoplakia. Histopathologically, there is a typical zonation or “tricolore” pattern with superficial eosinophilic parakeratosis in conjunction with a verrucous surface, a midepithelial pale zone of ballooned keratinocytes, and a basal zone of eosinophilic banal epithelia. EBER *in situ* hybridization shows Epstein–Barr virus in the superficial layer. There may be HPV co-infection.

References

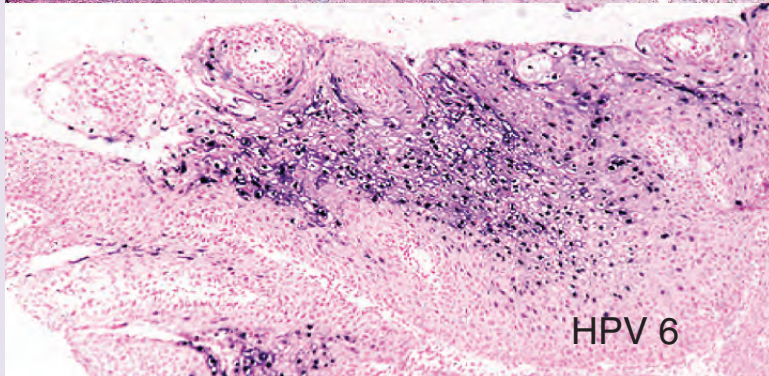
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- Grillo, E., Miguel-Morondo, A., Vano-Galvan, S., and Jaen-Olasolo, P. (2012) [Oral florid papillomatosis]. *Rev Clin Esp* **212**(11): e93.
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Buschke–Löwenstein Tumor (Giant Condyloma)

Exophytic lesion,
showing
verruciform
acanthosis and
papillomatosis



HPV6
In-situ
hybridization



BOWEN'S DISEASE

Cl: Large, almost cerebriform, foul-smelling papillomatous tumor, evolving from recurring and progressing small genital or perianal lesions.

Hi: Large condyloma, epithelial proliferation and dysplasia.

Reference

Zidar, N., Langner, C., Odar, K., et al. (2017) Anal verrucous carcinoma is not related to infection with human papillomaviruses and should be distinguished from giant condyloma (Buschke–Lowenstein tumour). *Histopathology* **70**(6): 938–45.

Malignant Epidermal Neoplasms

Bowen's Disease (Carcinoma *in situ*)

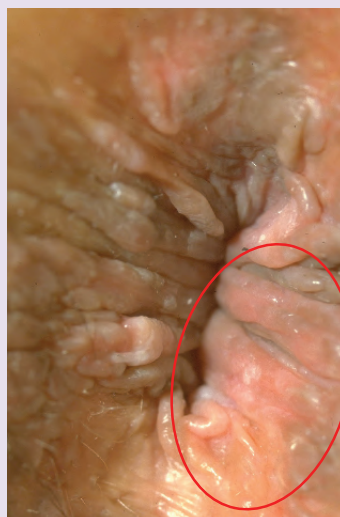
Psoriasiform and keratotic plaque on the trunk (left) and finger (right) respectively



Erythroplasia (Queyrat)

Sharply demarcated irregular plaque on the glans penis

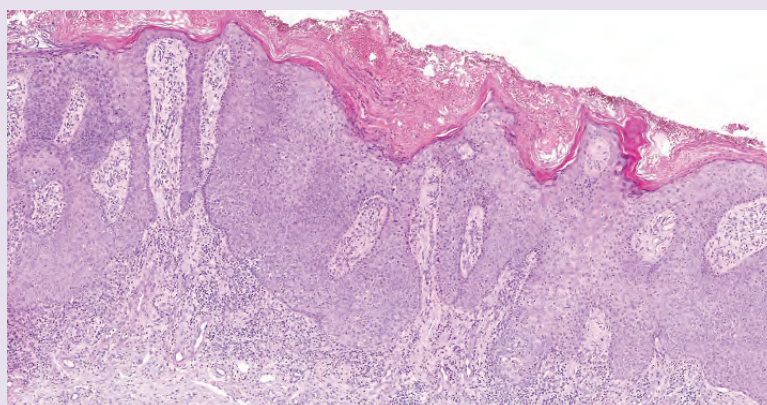
Plaque in the perianal region without sharp demarcation (circle)



BOWEN'S DISEASE

Bowen's Disease

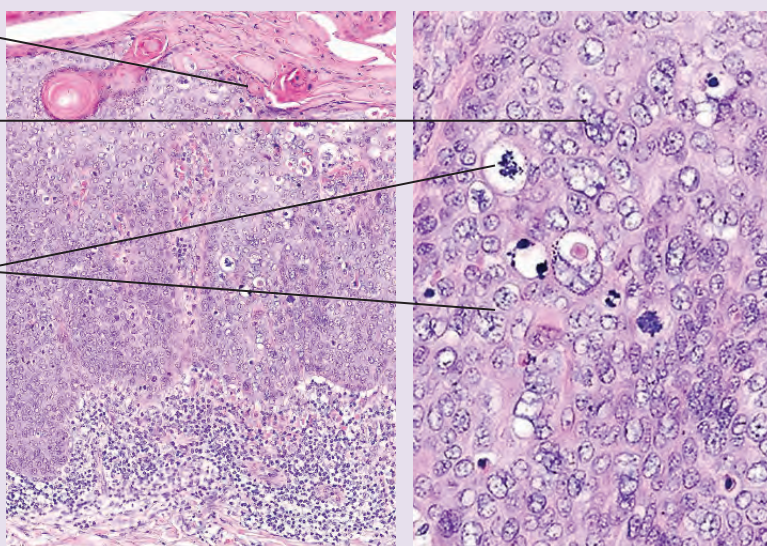
Hyperkeratotic, plump acanthosis and papillomatosis with epidermal dysplasia



Parakeratosis and dyskeratosis

"Crowded nuclei"

Atypical keratinocytes and mitoses



Cl: Flat, slowly expanding, psoriasiform, sharply bordered red or pink patch or plaque most frequently located on the trunk, but also at any other site of the body. Variants are erythroplasia of Queyrat at the male genitalia or pigmented Bowen's disease, preferentially in the anogenital region; the latter is often associated with HPV16/18 infection. Bowen's disease of the nailbed may be easily misdiagnosed.

Hi:

- Parahyperkeratosis and plump acanthosis
- The hallmarks are large, atypical, occasionally dyskeratotic multinucleated keratinocytes and many atypical mitotic figures, disseminated over all levels of the epidermis

- "Crowded nuclei"
- Preservation of a regular basal layer
- The tumor is *in situ* and does not cross the basement membrane. Invasive variants correspond to Bowen's carcinoma
- Tumor invasion into the epithelium of hair follicles and sweat glands may occur
- Clear cell type of Bowen's disease with multiple PAS-positive tumor cells may simulate Paget's disease

DD: Bowenoid actinic keratosis; bowenoid papulosis; superficial spreading melanoma; clonal seborrheic keratosis; pigmented Paget's disease of the mamilla.

BOWEN'S DISEASE

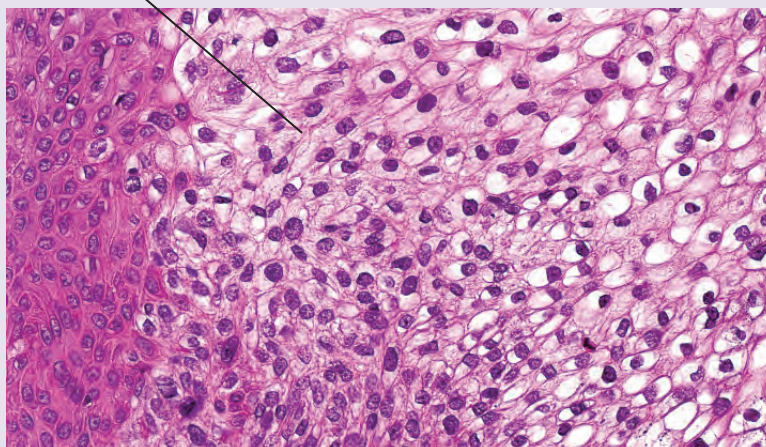
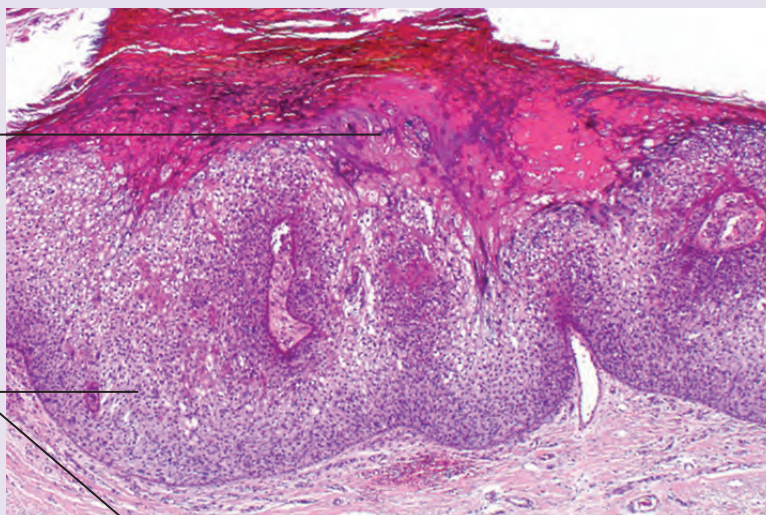
References

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- Idriss, M.H., Misri, R., and Boer-Auer, A. (2016) Orthokeratotic Bowen disease: a histopathologic, immunohistochemical and molecular study. *J Cutan Pathol* **43**(1): 24–31.
- Kalegowda, I.Y. and Boer-Auer, A. (2017) Clonal seborrheic keratosis versus pagetoid bowen disease: histopathology and role of adjunctive markers. *Am J Dermatopathol* **39**(6): 433–9.
- Kogut, M., Toberer, F., Enk, A.H., and Hassel, J.C. (2016) Limitations of Ber-EP4 for distinction of Bowen disease from basal cell carcinoma. *J Cutan Pathol* **43**(4): 367–71.
- Svajdler, M. Jr, Mezencev, R., Kaspirkova, J., et al. (2016) Human papillomavirus infection and p16 expression in extragenital/extraungual bowen disease in immunocompromised patients. *Am J Dermatopathol* **38**(10): 751–7.
- Takayama, R., Ishiwata, T., Ansai, S., et al. (2013) Lumican as a novel marker for differential diagnosis of Bowen disease and actinic keratosis. *Am J Dermatopathol* **35**(8): 827–32.

Variant: Clear Cell Bowen's Disease

Hyperkeratosis
and
dyskeratosis

Pale
glycogen-rich
keratinocytes

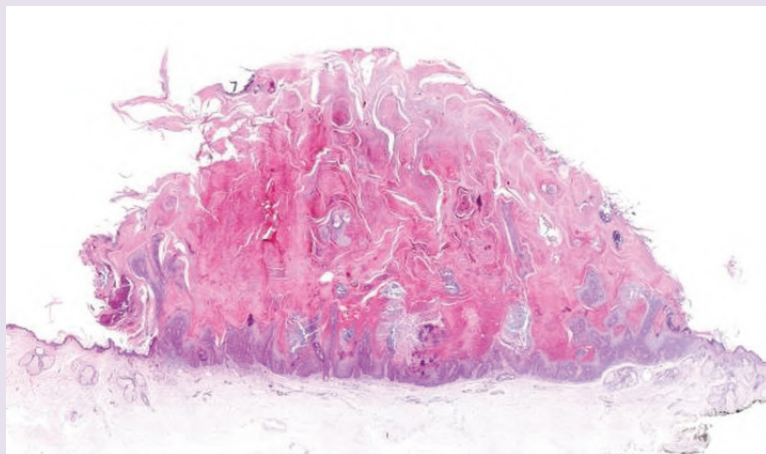


BOWEN'S DISEASE

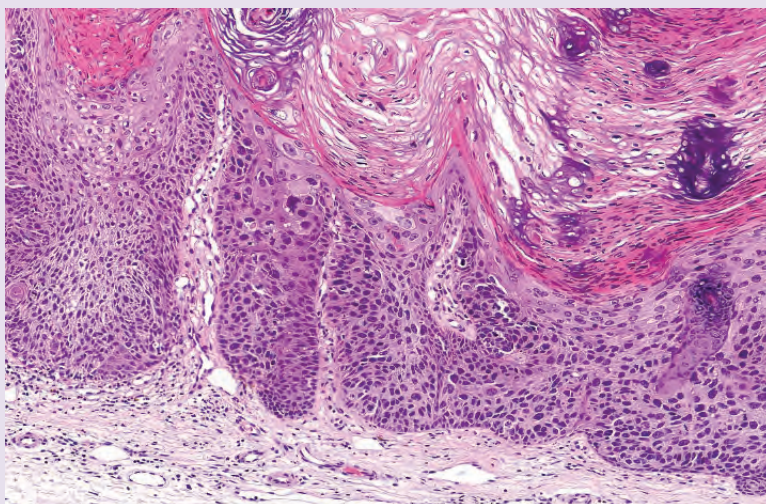
Hi: Pale keratinocytes with PAS-positive glycogen-rich cytoplasm.

Variant: Cutaneous Horn (Cornu Cutaneum) on Bowen's Disease

Pyramid-like hyperkeratosis



Bowen's disease (carcinoma in-situ) underlying cutaneous horn



Cl: Morphological term, describing a keratotic exophytic tumorous lesion, originating from various conditions, including Bowen's disease, actinic keratosis, squamous cell carcinoma.

Hi:

- Pyramid-shaped hyperkeratosis

- At the base histological features of Bowen's disease

DD: Cutaneous horn on actinic keratosis; warty dyskeratoma; squamous cell carcinoma; lupus erythematosus.

BOWEN'S DISEASE

Reference

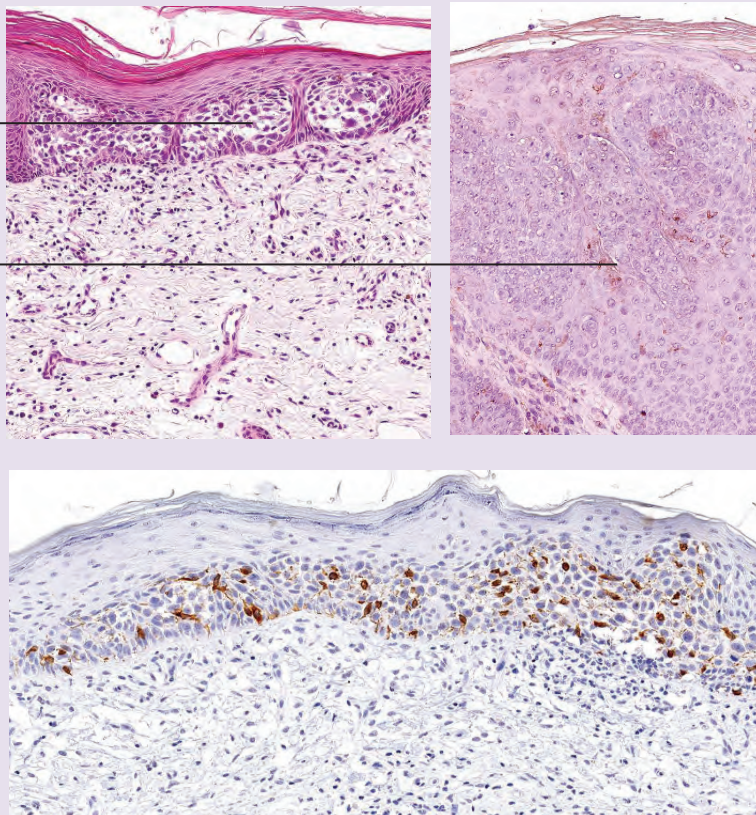
Lora, V., Scarabello, A., and Cota, C. (2015) Warty dyskeratoma as a cutaneous horn of the mons pubis. *Am J Dermatopathol* 37(10): 802–4.

Variant: Pigmented (Anogenital) and Clonal Bowen's Disease

Nests of
intraepidermal
(clonal)
Bowenoid cells

Melanin in
Bowen's
disease

Melan A-staining
of melanocytes
in pigmented
Bowen's disease



CI: Bowen's disease in the anogenital region frequently is pigmented, especially in dark-skinned individuals. Most cases are associated with oncogenic HPV infection (HPV16, HPV18).

Hi:

- Hyperpigmented bowenoid keratinocytes

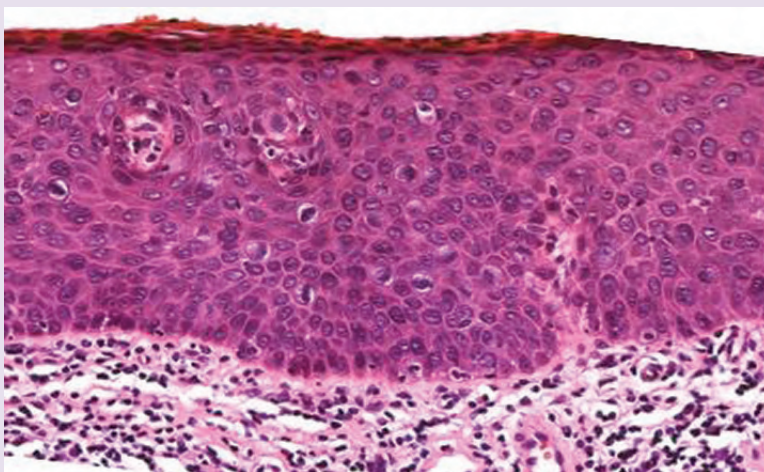
- Atypical keratinocytes are AE1/AE3 positive but CK7 negative
- Slightly increased number of Melan A-positive melanocytes

BOWEN'S DISEASE**Variant: Erythroplasia of Queyrat and Vulvar Intraepithelial Neoplasia**

Glans penis

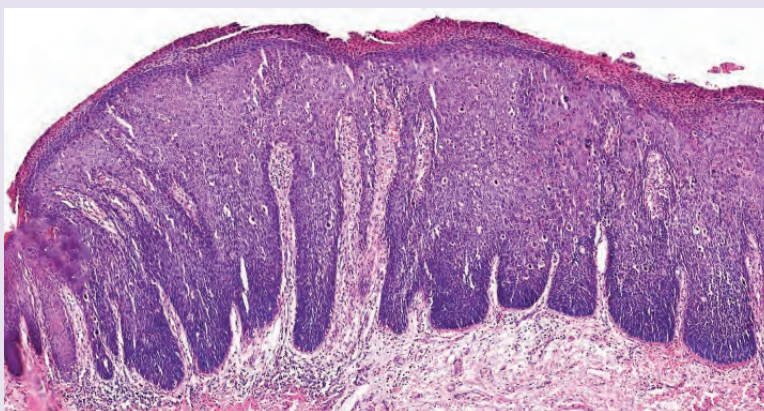
Acanthosis,
bowenoid cells
in all levels of
the epidermis

Inflammatory
infiltrate,
containing many
plasma cells

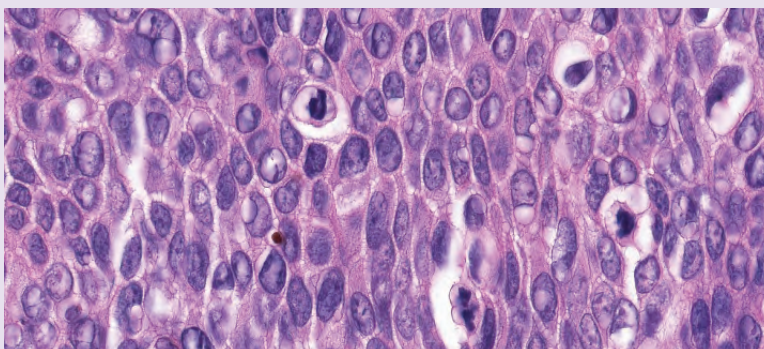


Vulva

Acanthosis,
papillomatosis



Bowenoid cells
with marked
pleomorphism
and mitoses



BASAL CELL CARCINOMA

Cl: Red, velvety, sharply bordered irregular patch or plaque on the glans penis. Similar lesions can be found in anogenital localisations and oral mucosa of both sexes. By some authors, Queyrat's disease is considered to be a separate entity with a worse prognosis rather than a variant of Bowen's disease.

Hi:

- Superficial erosion
- Slight acanthosis and/or papillomatosis

- Minimal dyskeratosis
- Atypical "bowenoid" keratinocytes in all levels of the epidermis
- Inflammatory infiltrate on the basis of the lesion, containing many plasma cells

Basal Cell Carcinoma (BCC)

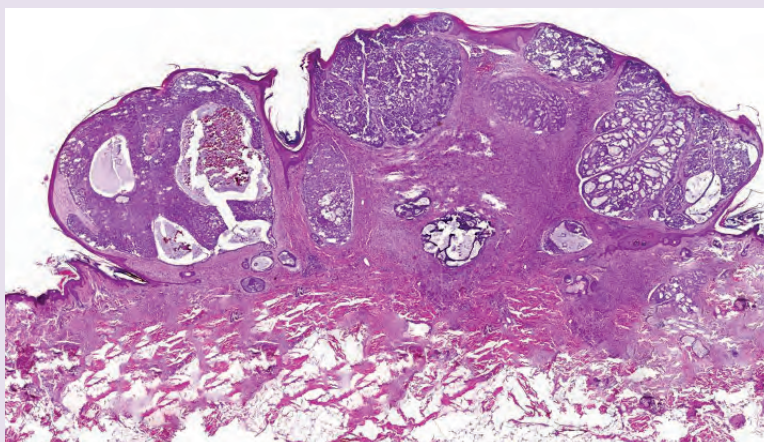
Many variants exist.

Variant: Nodular BCC

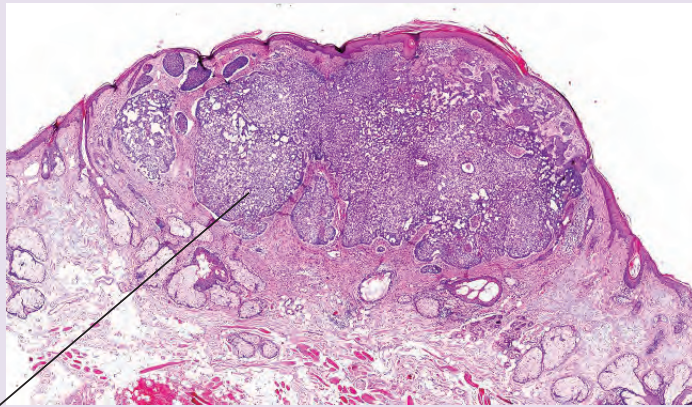
Pearly, waxy tumor with elevated border and telangiectases



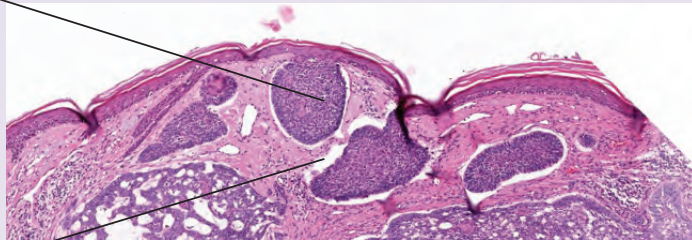
Exophytic proliferation of basaloid cells



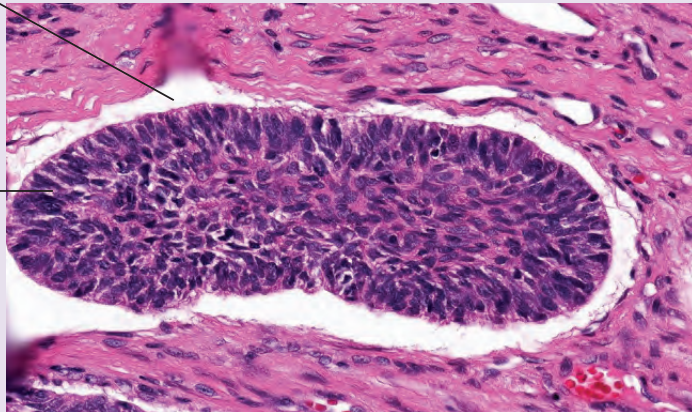
Variant: Nodular BCC



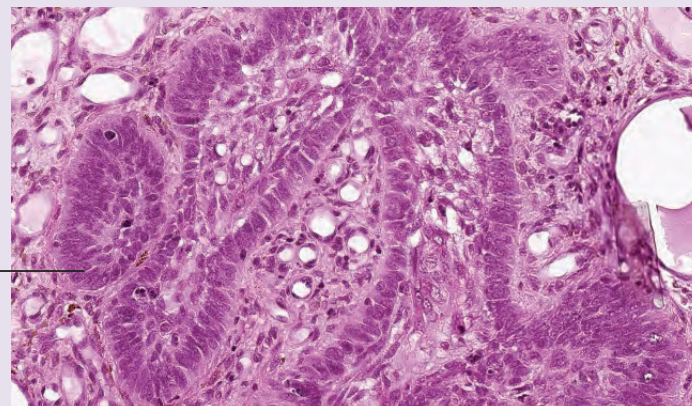
Proliferation of basaloid cells connected with the epidermis



Artificial cleft formation at the margin of tumor nodules



Peripheral palisading arrangement of basaloid cells



Peripheral palisading

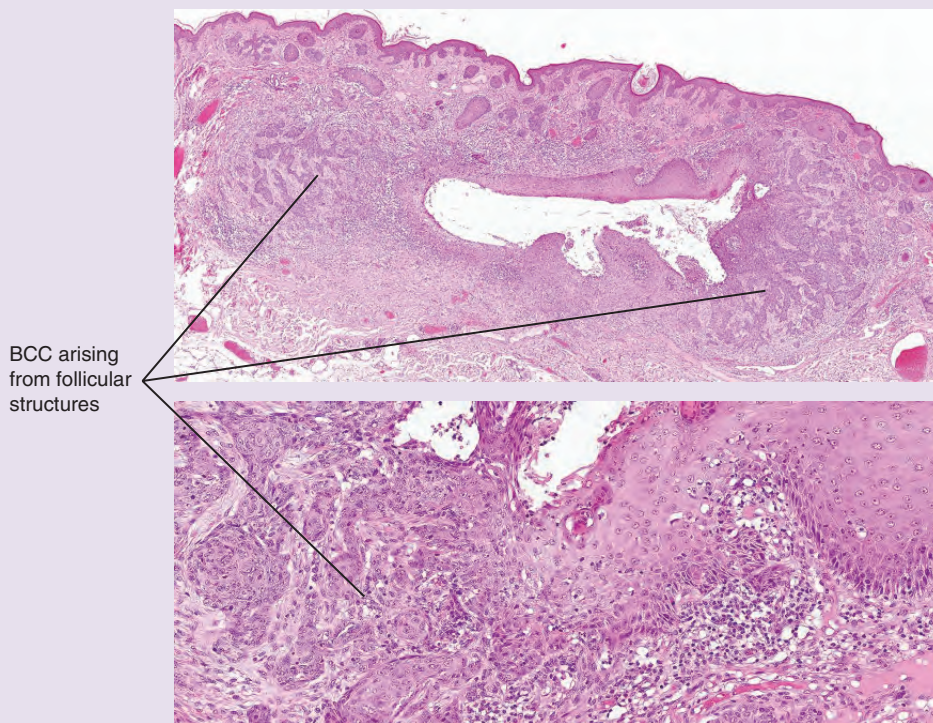
BASAL CELL CARCINOMA

Cl: Pink or red well-circumscribed nodule, preferentially localized in sun-exposed skin. Pearly or waxy elevated border, telangiectases. Often central superficial erosion and crust formation.

Hi:

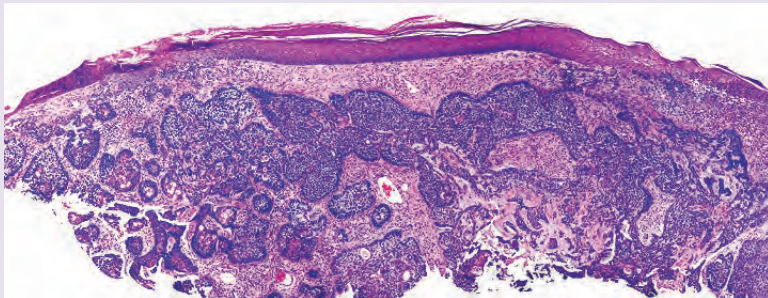
- Basophilic roundish and oval-shaped epithelial cells
- Peripheral band-like palisading arrangement
- Connection between tumor and epidermis or adnexa
- Prominent shrinkage clefts between tumor and surrounding stroma
- Immunohistochemical expression of BerEP4

Variant: Infundibulocystic BCC

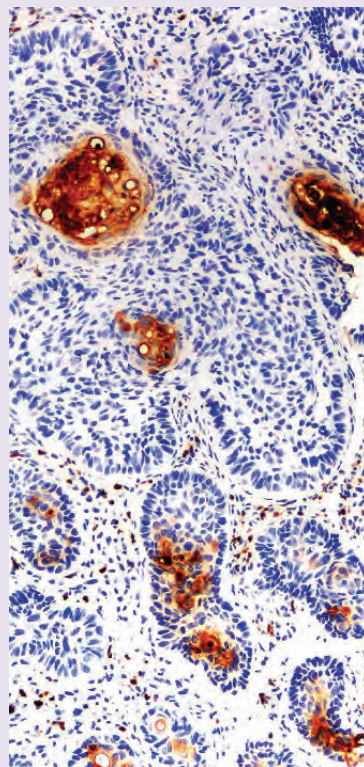
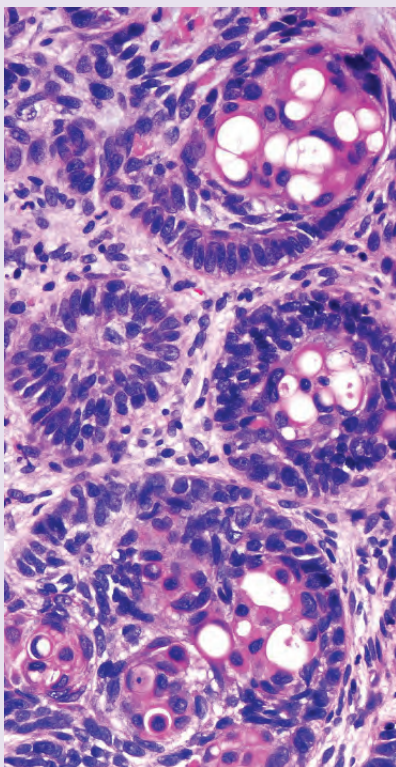


Cl: No specific clinical appearance.

Hi: Proliferation of basaloid cells, originating from follicular structures.

BASAL CELL CARCINOMA**Variants of BCC With Ductal, Matrical or Sebaceous Differentiation****Variant: BCC with Ductal Differentiation**

BCC with ductal
structures;
CEA-positive

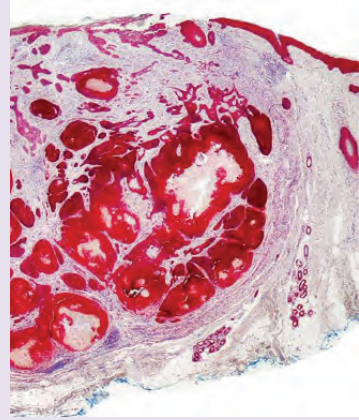
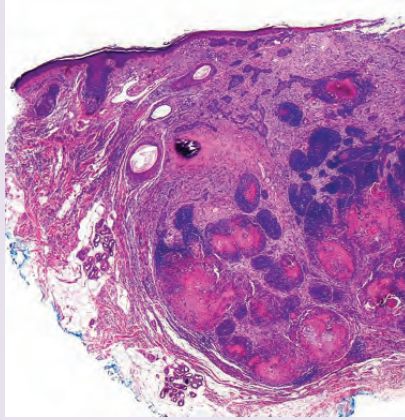


Courtesy of Luis Requena, Madrid

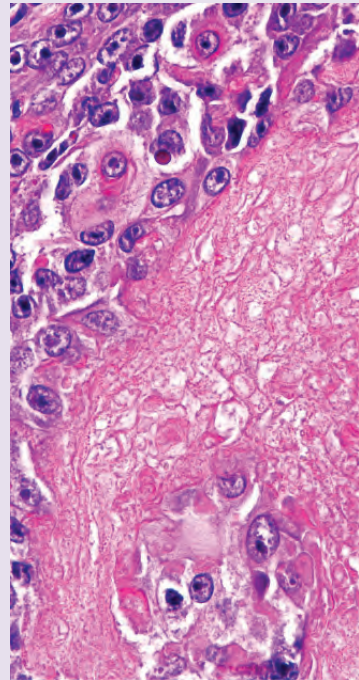
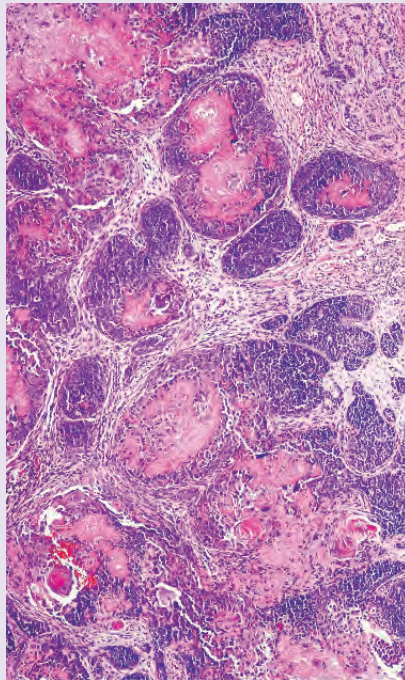
BASAL CELL CARCINOMA

Variant: BCC with Matrical Differentiation

BCC with matrical differentiation; beta-catenin (right)



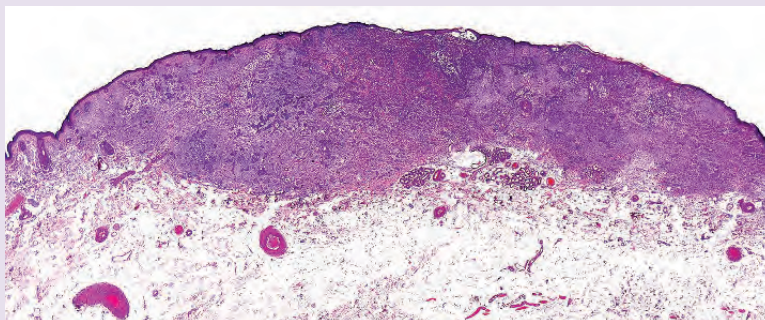
Nests of basaloid cells; shadow cells (right)



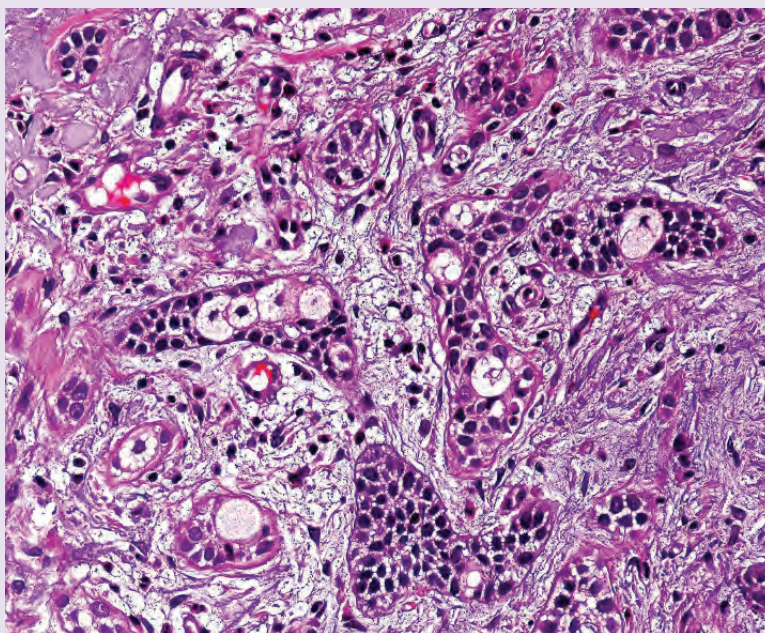
Courtesy of Luis Requena, Madrid

BASAL CELL CARCINOMA**Variant: BCC with Sebaceous Differentiation**

BCC with strong
fibrous stroma
reaction



Nests of
basaloid cells
with sebaceous
differentiation



Courtesy of Luis Requena, Madrid

Comment: Distinct differentiation towards various structures may be seen in some BCC, which sometimes leads to diagnostic pitfalls.

References

- Ambrojo, P., Aguilar, A., Simon, P., Requena, L., and Sanchez Yus, E. (1992) Basal cell carcinoma with matrical differentiation. *Am J Dermatopathol* **14**(4): 293–7.
- Del Sordo, R., Cavaliere, A., and Sidoni, A. (2007) Basal cell carcinoma with matrical differentiation: expression of beta-catenin [corrected] and osteopontin. *Am J Dermatopathol* **29**(5): 470–4.

BASAL CELL CARCINOMA

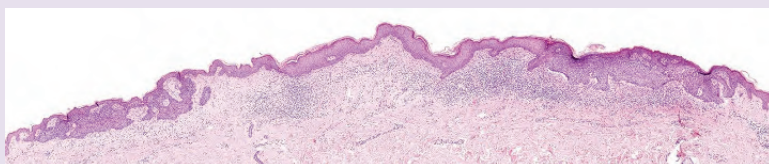
Variant: Superficial BCC

Left: multiple superficial BCCs

Right: pigmented superficial BCC

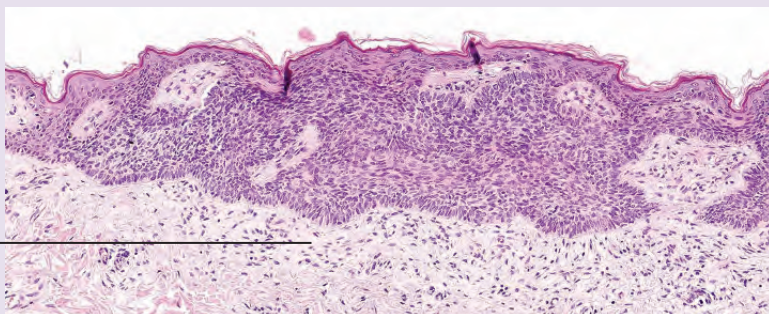


Multicentric nests attached to the epidermis



Superficial BCC

Mucin in the surrounding stroma



Cl: Solitary or multiple plaques; mostly located on the trunk.

Hi:

- Solitary or confluent superficial nests of basaloid epithelial cells
- Connection with the epidermis or with adnexal structures

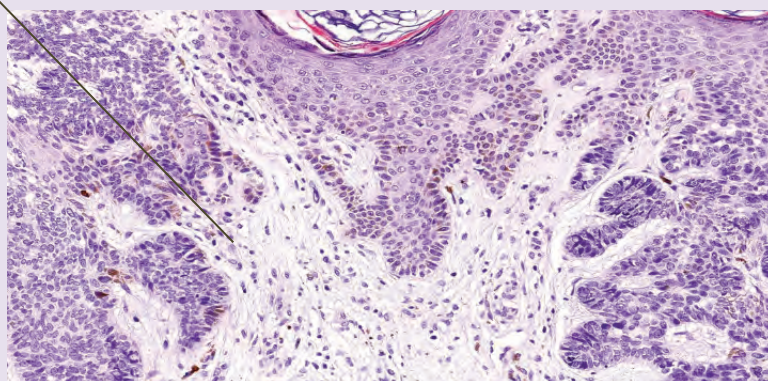
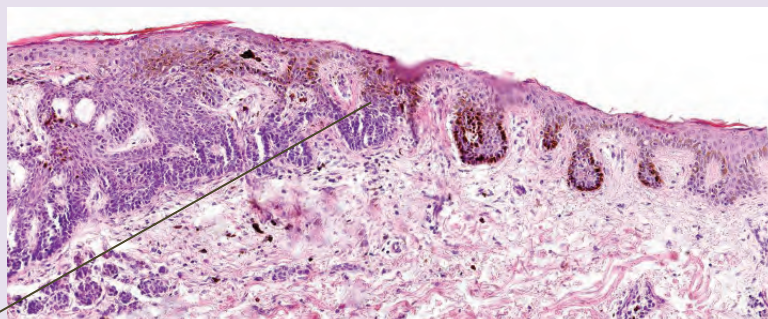
- Peripheral palisading
- Distinct shrinkage clefts
- Adjacent tumor stroma containing mucin
- Fibrosis and inflammatory infiltrate in the upper dermis

BASAL CELL CARCINOMA**Variant: Pigmented BCC**

Pigmented
nodular BCC



Melanin deposits
in basaloid cells
and in
melanophages
in the surrounding
stroma



Cl: Nodular or superficial pigmented lesion.

Hi: Increased number of intratumoral melanocytes in scattered array.

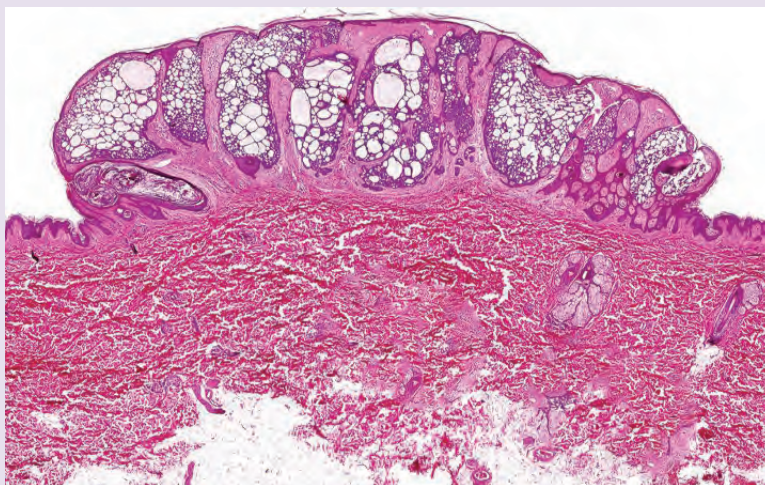
BASAL CELL CARCINOMA

Variant: Adenoid-Cystic BCC

Adenoid-cystic BCC, originating from the lower eyelid



Tumor from the trunk. Fenestrated tumor pattern. Intralesional cystic spaces



CI: Single or multiple confluent soft, translucent bluish-white nodules with discrete telangiectases. Preferential localisation is the eyelids. Hidrocystoma is the most common differential diagnosis.

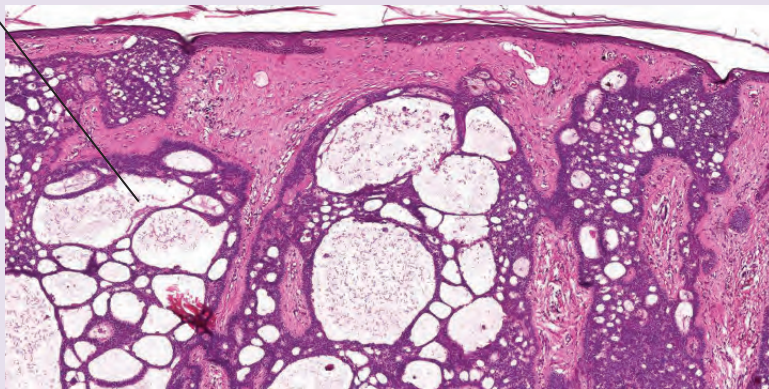
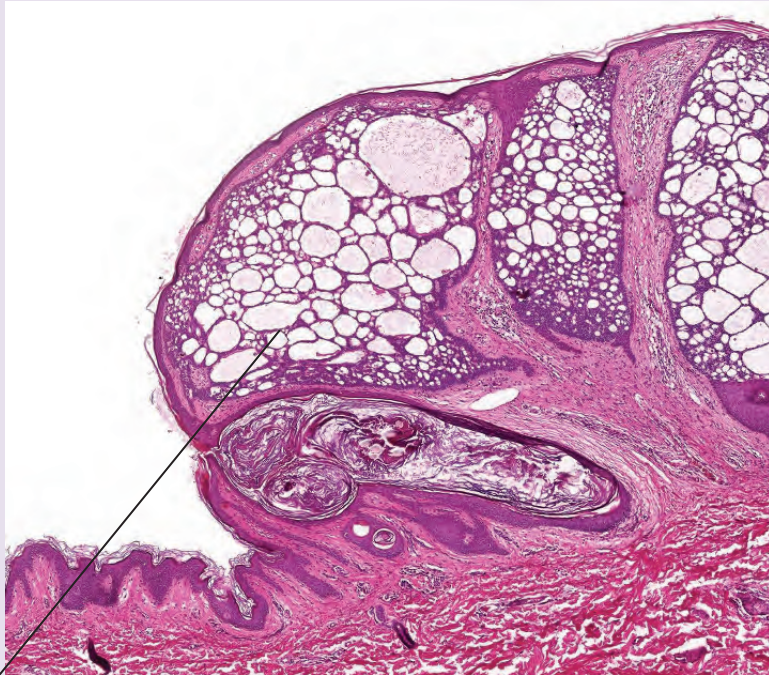
Hi: Solid nodules of basaloid cells and intratumoral mucin-filled cystic spaces.

DD: Mucinous eccrine carcinoma, showing slender strands of basaloid epithelial cells lying in

“puddles of mucin.” Endocrine mucin-producing tumor (as a variant of mucinous eccrine carcinoma) presenting with roundish basaloid tumor nests in a “cannonball”-like arrangement. Nests may contain intratumoral mucinous lakes. Characteristic immunophenotype with expression of chromogranin, synaptophysin, estrogen, and progesterone.

BASAL CELL CARCINOMA**Variant: Adenoid-Cystic BCC**

Exophytic lesion
with intratumoral
cystic spaces



BASAL CELL CARCINOMA

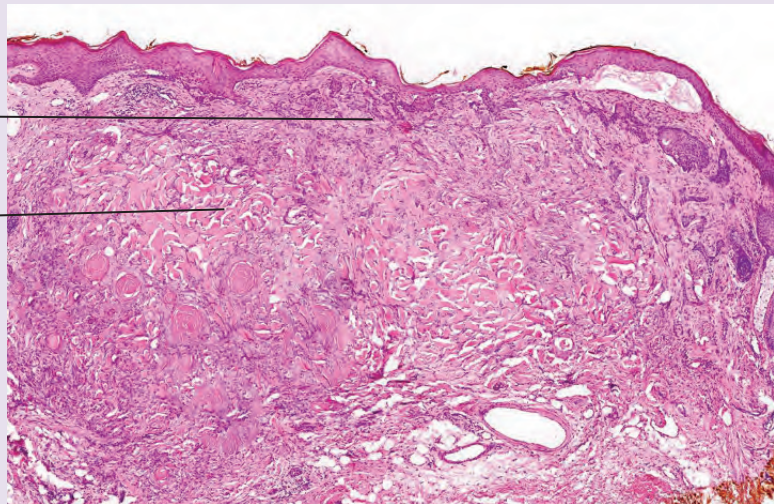
Variant: Sclerodermiform (Morpheaform) BCC

Slightly atrophic superficial lesions on the nose (left) and forehead (right)



Delicate tumor strands within sclerotic stroma

Sclerosis between and underneath tumor islands



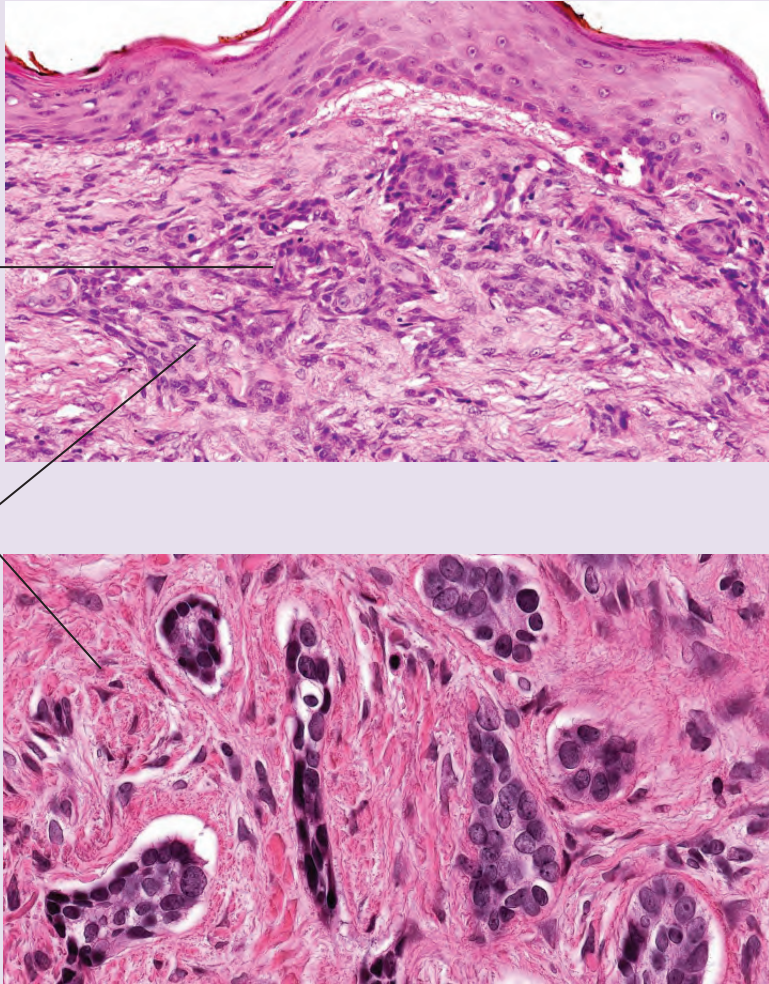
BASAL CELL CARCINOMA

Variant: Sclerodermiform (Morpheaform) BCC

Elongated thin
tumor strands
and nests

Fibrosis and
sclerosis
between
and beneath
tumor strands

Tumor nests
of various sizes
and shapes



Cl: Poorly circumscribed indurated scar-like lesion. Spread beyond clinically recognizable borders. Aggressive course, especially in the nasolabial fold, where deeper structures may be involved. Ulceration is rare.

Hi:

- Small thin tumor islands and strands, proliferating between collagen bundles

- Absence of peripheral palisading
- Fibrosis of the surrounding dermis
- Cleft formation may occur, but is not typical
- Strong positivity for BerEP4

DD: Clinical differential diagnoses include traumatic scar, morphea, desmoplastic melanoma, desmoplastic trichoepithelioma, microcystic adnexal carcinoma.

BASAL CELL CARCINOMA

Clinical Variants: Ulcerating BCCs

Ulcus rodens



Ulcus terebrans

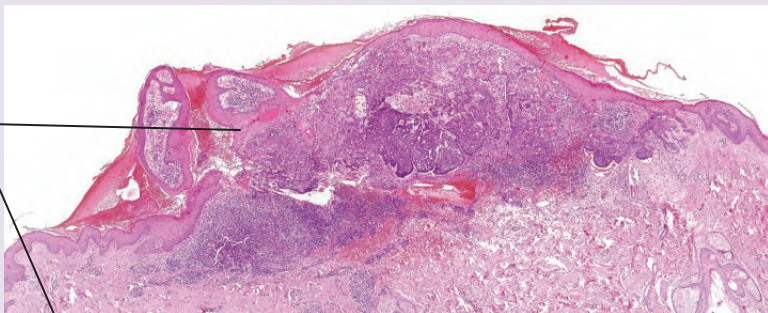


Two types can be differentiated, both with an aggressive clinical course. Ulcus rodens ulcerates and spreads peripherally, whereas ulcus terebrans

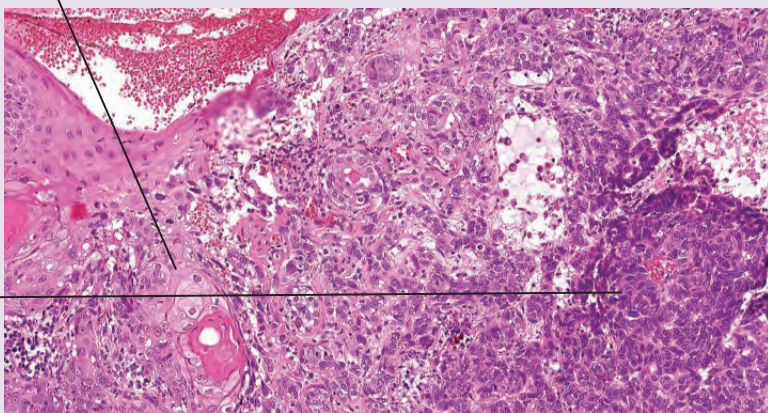
spreads into the depth, destroying underlying structures, including cartilage and bone.

BASAL CELL CARCINOMA**Histological Variants: Metatypic BCC with Squamoid Differentiation**

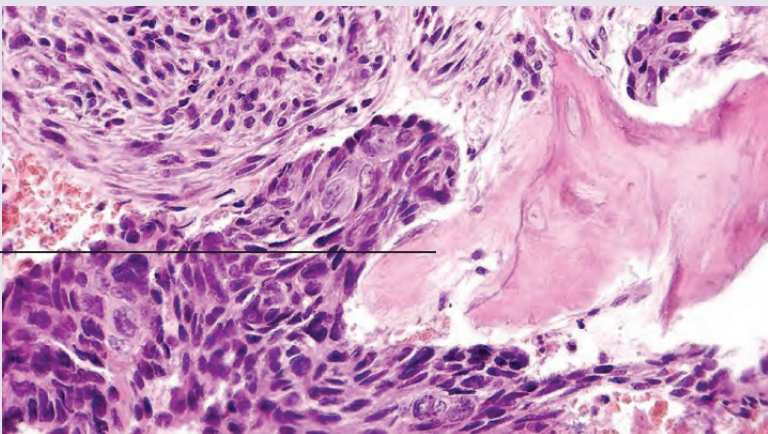
Predominant
BCC pattern with
focal squamoid
differentiation



BCC tumor
nests

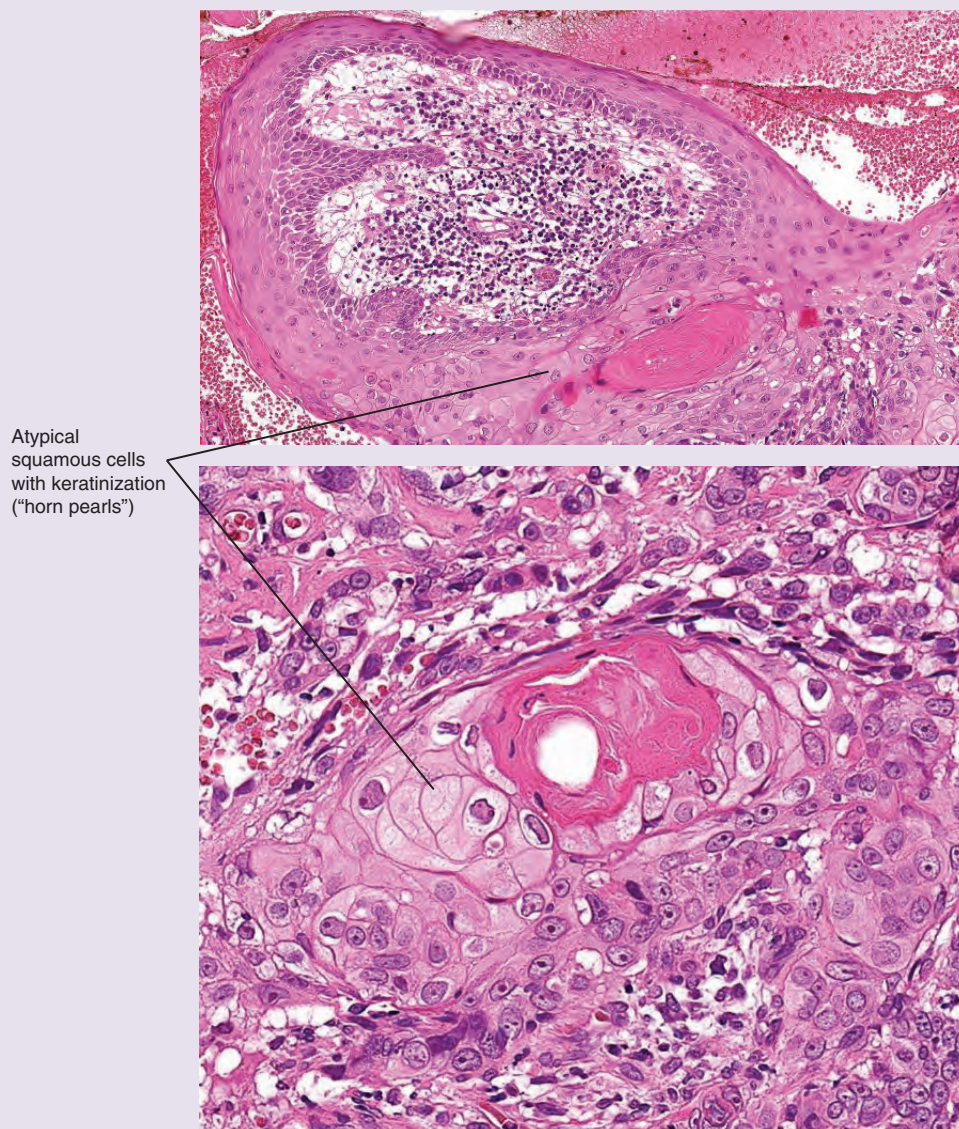


Metaplastic
bone



BASAL CELL CARCINOMA

Variant: Metatypic BCC with Squamoid Differentiation



Hi: Cytological features indeterminate between classic basal cell carcinoma and squamous cell carcinoma. Often with typical basaloid tumor

formation blending into squamous cell carcinoma-like zones of differentiation.

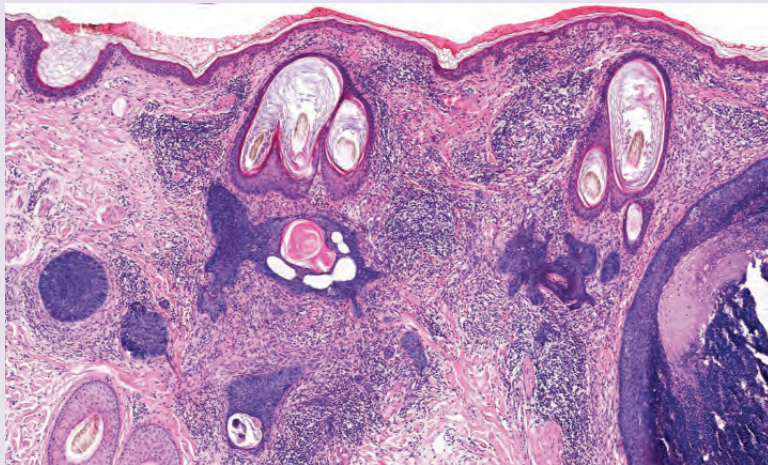
Syndromic BCC (Basal Cell Nevus Syndrome, Gorlin–Goltz)

Multiple BCCs
on the scalp

Palmar pits
(circle)



Proliferation
of basaloid cells
originating from
infundibulocystic
structures



Several syndromes are associated with increased risk of BCC: Bazex–Dupré–Christol syndrome, Rombo syndrome, multiple hereditary infundibulocystic basal cell carcinomas, basaloid follicular hamartoma.

CI: Autosomal dominant inherited mutation of the PTCH gene, which is responsible for disorders affecting the skin, skeleton, and central nervous system. Patients develop multiple basal cell carcinomas disseminated over trunk, face, and

extremities. Initially, BCC may resemble small melanocytic nevi, before developing into larger BCCs. As in non-syndromic BCCs, UV light and x-rays are promoting factors. Additional clinical signs include palmar pits (tiny defects of the stratum corneum), mandibular cysts, kyphoscoliosis, and calcified falx cerebri.

Hi: Corresponds to sporadic BCC. Most commonly nodular or superficial subtype. Early lesions may show an infundibulocystic origin.

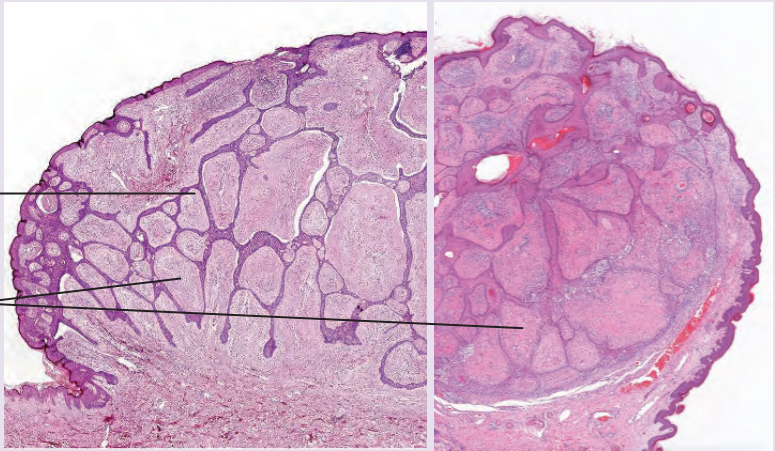
Fibroepithelioma of Pinkus

Fibroepithelioma
of Pinkus (left)
adjacent to
superficial BCC
(right)



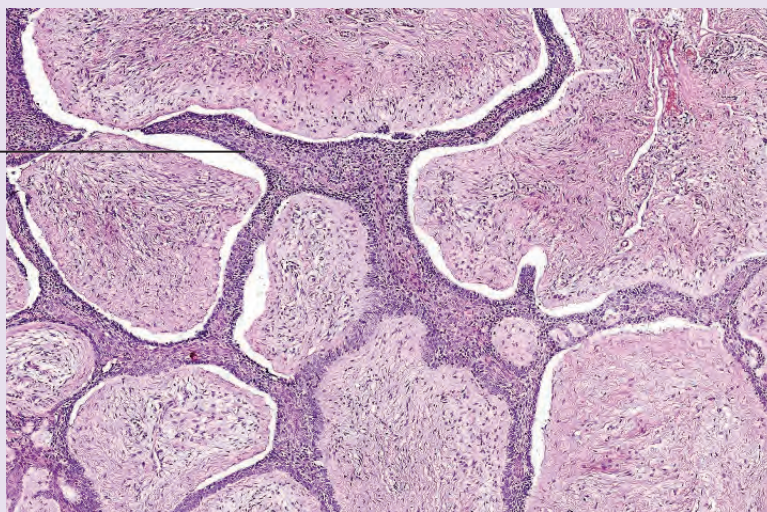
Reticulate
strands of tumor
epithelium

Fibromucinous
stroma

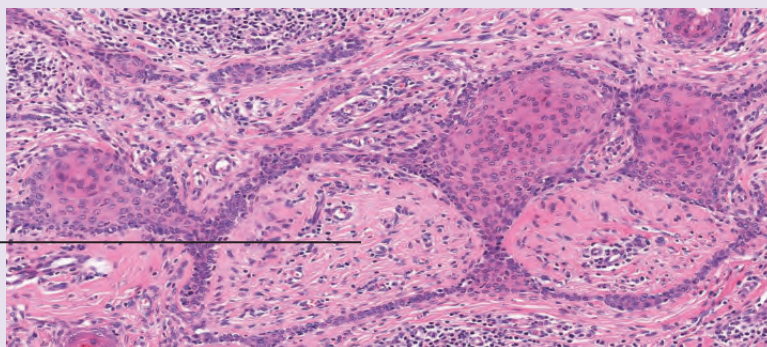


Fibroepithelioma of Pinkus

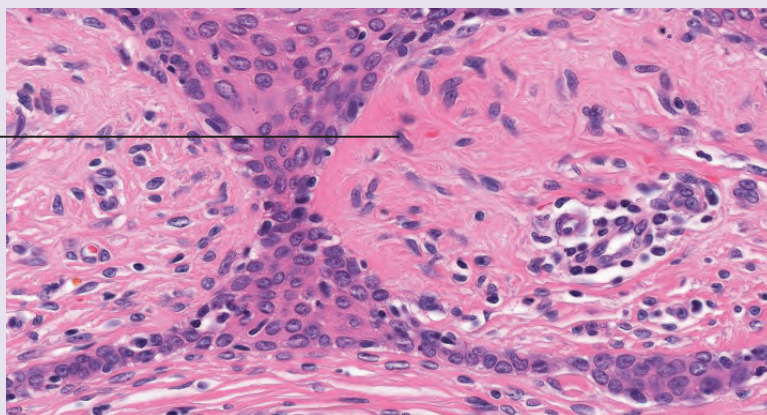
Reticulate
anastomosing
strands of tumor
epithelium.
Typical
peritumoral clefts



Fibrotic stroma



Epithelial
amyloid



Cl: Soft nodular, non-ulcerating lesion, preferentially in lumbosacral localisation.

Hi: Fibroepithelioma of Pinkus is considered to be a reticulated variant of BCC.

- Lacy strands of tumorous epithelium
- Connection with the epidermis
- Prominent fibromucinous stroma
- Peritumoral shrinkage clefts and peripheral palisading may be focally present
- At the tips of elongated tumor strands, there may be small, nub-like BerEP4-positive basalioid nests considered to be indicators of abortive hair bulb formation
- Focal positivity for PHLDA-1

SQUAMOUS CELL CARCINOMA

References

- Bowen, A.R. and LeBoit, P.E. (2005) Fibroepithelioma of Pinkus is a fenestrated trichoblastoma. *Am J Dermatopathol* **27**(2): 149–54.
- Katona, T.M., Ravis, S.M., Perkins, S.M., Moores, W.B., and Billings, S.D. (2007) Expression of androgen receptor by fibroepithelioma of Pinkus: evidence supporting classification as a basal cell carcinoma variant? *Am J Dermatopathol* **29**(1): 7–12.
- Naeyaert, J.M., Pauwels, C., Geerts, M.L., and Verplancke, P. (2001) CD-34 and Ki-67 staining

patterns of basaloid follicular hamartoma are different from those in fibroepithelioma of Pinkus and other variants of basal cell carcinoma. *J Cutan Pathol* **28**(10): 538–41.

- Stern, J.B., Haupt, H.M., and Smith, R.R. (1994) Fibroepithelioma of Pinkus. Eccrine duct spread of basal cell carcinoma. *Am J Dermatopathol* **16**(6): 585–7.

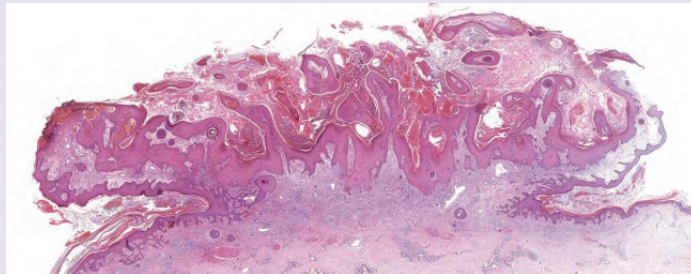
Squamous Cell Carcinoma (SCC)

Variant: Well-Differentiated SCC

Tumor with hyperkeratotic crust

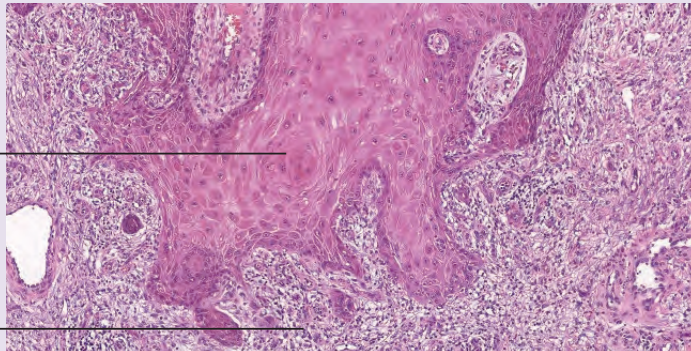


Exophytic proliferation of tumor cells



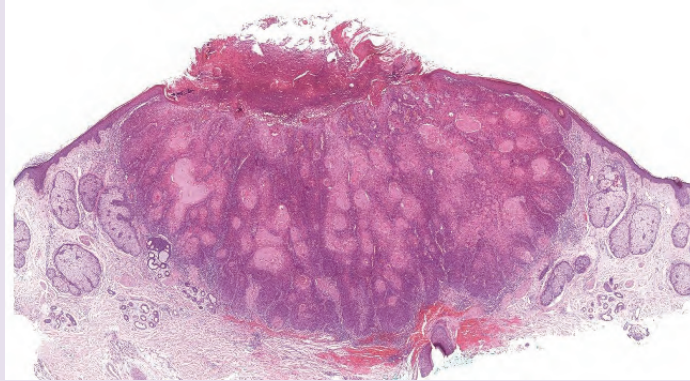
Pseudopod-like proliferation of atypical keratinocytes with islands of keratinization

Tumor stroma with inflammatory infiltrate and fibrosis

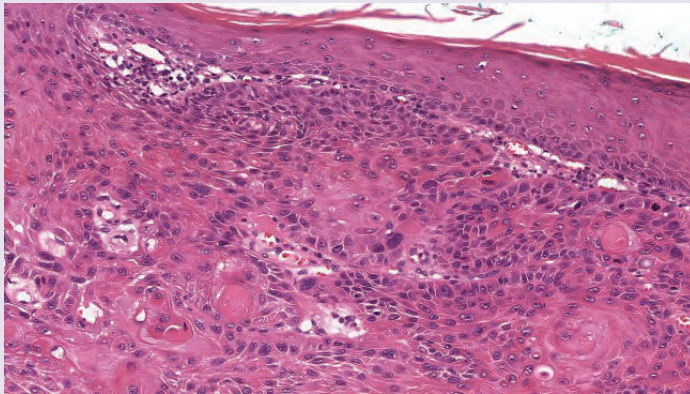


SQUAMOUS CELL CARCINOMA**Variant: Well-Differentiated SCC**

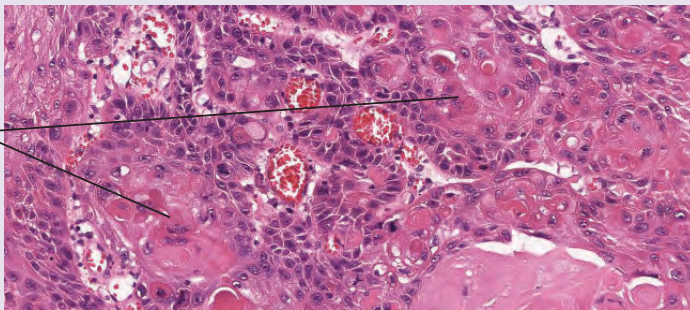
Endophytic tumor with hyperkeratotic crust



Proliferation of atypical keratinocytes



Horn pearls



Cl: SCCs usually arise on chronically damaged skin (UV or ionizing irradiation, scars from wounds, burning, chronic ulcers, fistulae, lupus erythematosus, lupus vulgaris). They can appear anywhere on the body, including lips, tongue, and anogenital region. The lower third of the face, lower lip, earlobe, and dorsa of the hands are favored sites. The firm, nodular plaques are usually covered with hyperkeratotic crusts. Well-differentiated, highly

keratinizing SCCs have an intermediate malignant potential with a low tendency to metastasize.

Hi:

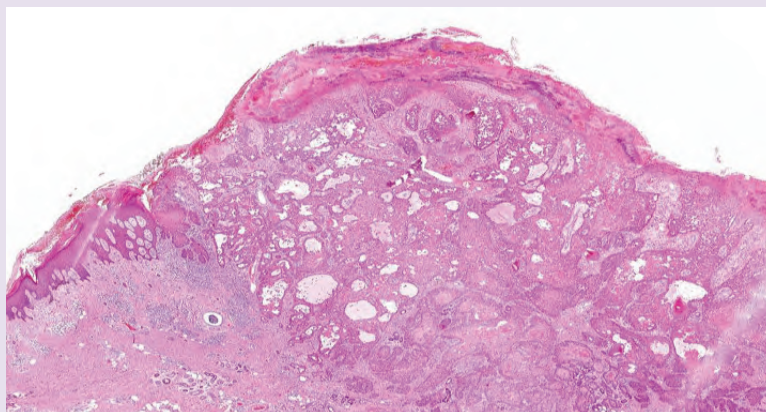
- Invasive epithelial tumor with asymmetry and poor circumscription
- Proliferation of pleomorphic epithelial tumor cells, corresponding to the keratinocytes of the spinous layer of the epidermis
- Eosinophilic cytoplasm

SQUAMOUS CELL CARCINOMA

- Intercellular bridges
- Focal keratinization and horn pearls
- Mitoses
- Focal necroses, not as pronounced as in keratoacanthoma
- Infiltrative growth
- Sometimes tumoral acantholysis may be present, simulating pattern of angiosarcoma

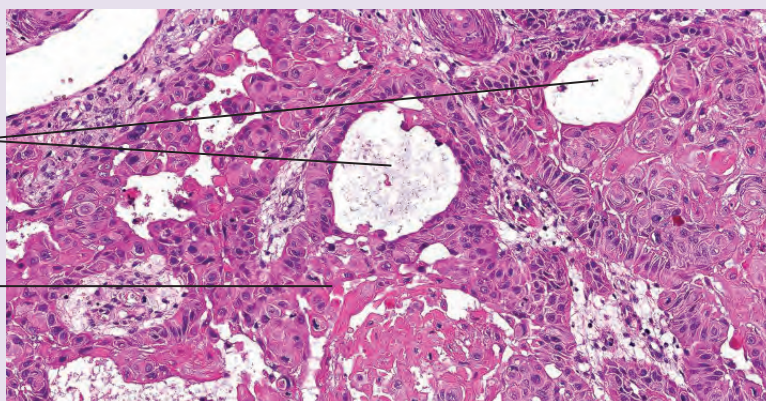
Variant: Acantholytic SCC (Epithelioma Spinocellulare Segregans of Delacretaz)

Squamous cell tumor with many cystic spaces

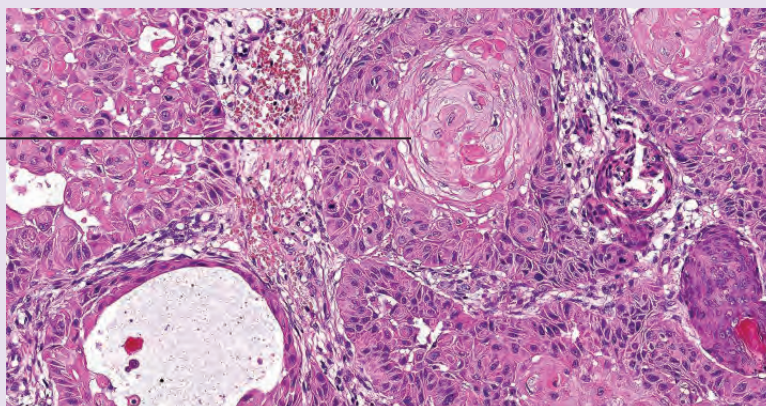


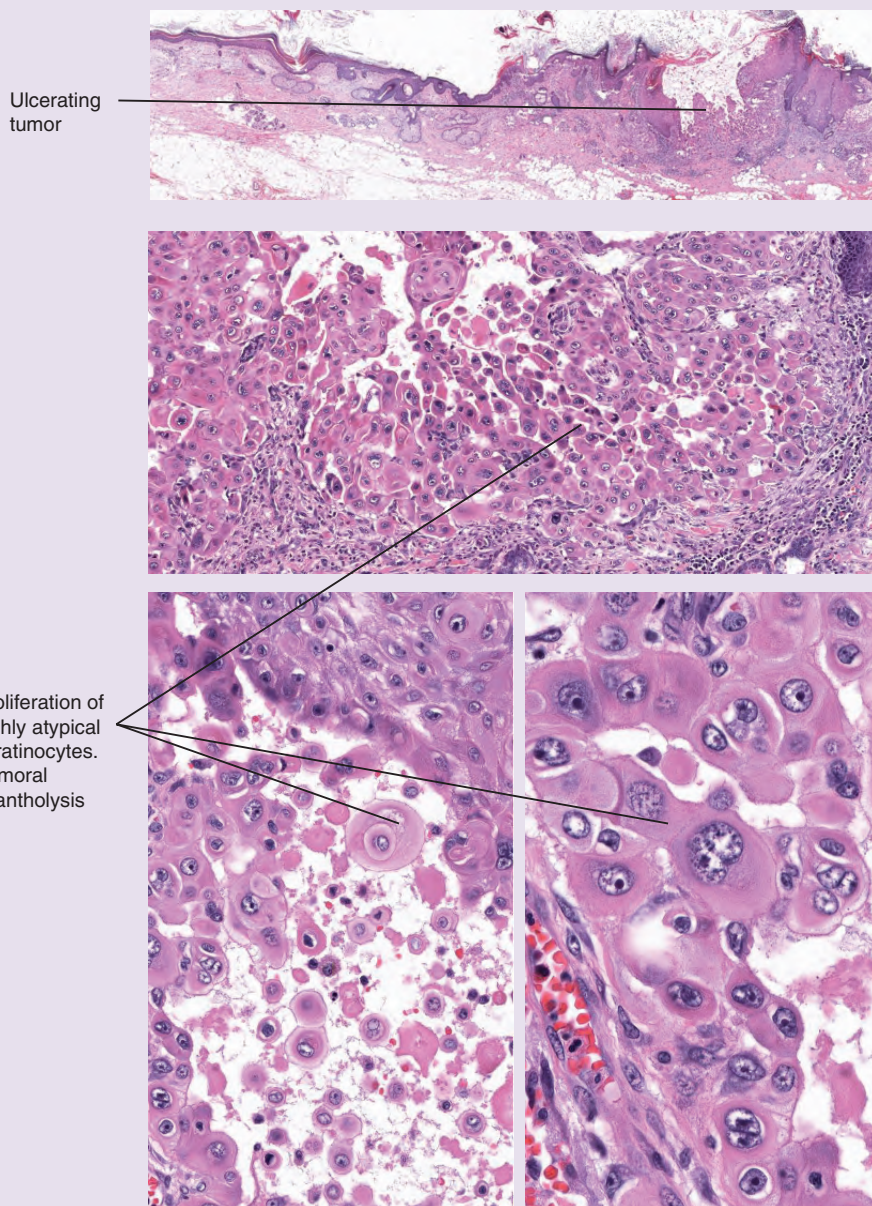
Cysts

Acantholysis



Squamous eddy



SQUAMOUS CELL CARCINOMA**Variant: Acantholytic SCC (Epithelioma Spinocellulare Segregans of Delacretaz)**

This is not an entity in its own right but rather a poorly differentiated SCC variant with free-floating keratinocytes. Intercellular adhesion has been lost throughout the entire tumor, resulting in an angiosarcoma-like tumor pattern (tumoral acantholysis). **CI:** Minimal hyperkeratosis. Mostly ulcerated, bleeding or oozing, crust formation.

Hi:

- Pleomorphic and anaplastic keratinocytes
- Loss of intercellular bridges with acantholysis
- Inflammatory infiltrate, often containing many plasma cells

SQUAMOUS CELL CARCINOMA

Reference

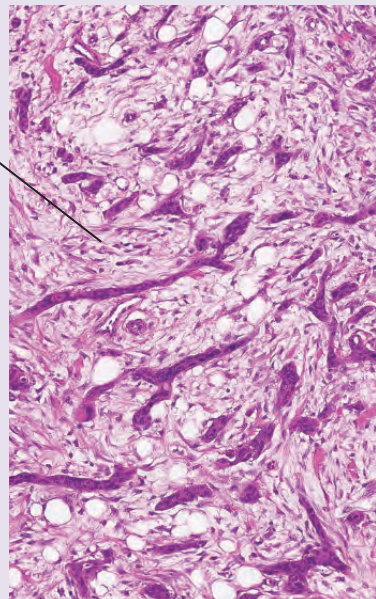
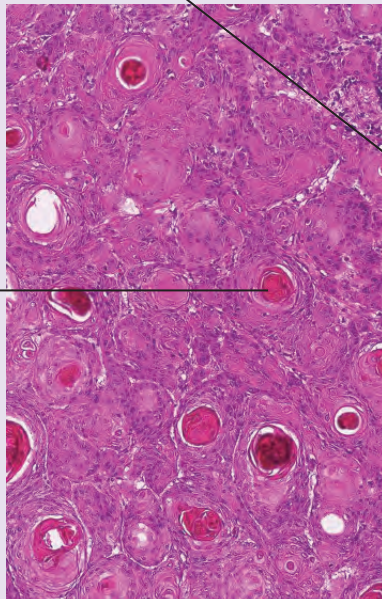
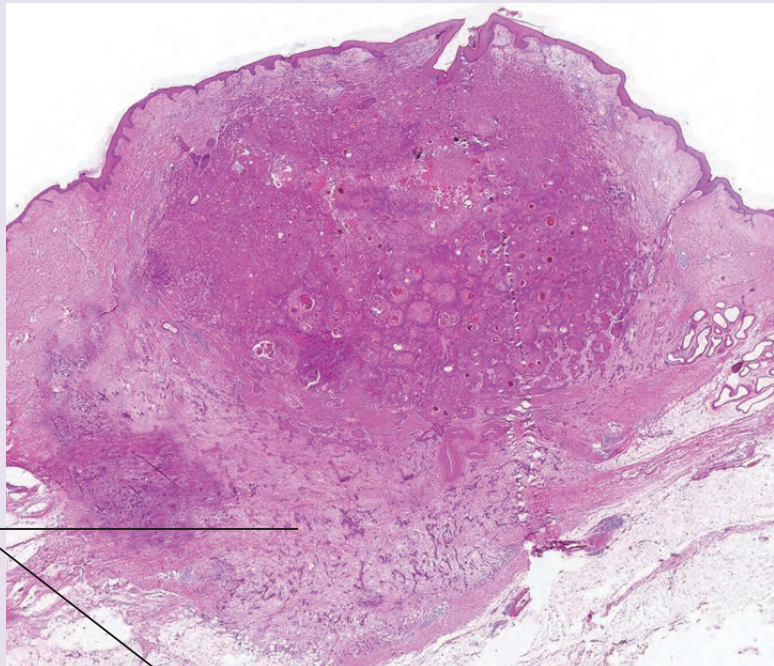
Delacretaz, J., Madjedi, A.S., and Loretan, R.M. (1957)
[Epithelioma spinocellulare segregans; the so-called
adenoacanthoma of the sweat glands (Lever)].
Hautarzt **8**(11): 512–18.

Variant: Myxoid SCC

Nodular
proliferation
with contiguous
solid (above) and
myxoid (below)
components

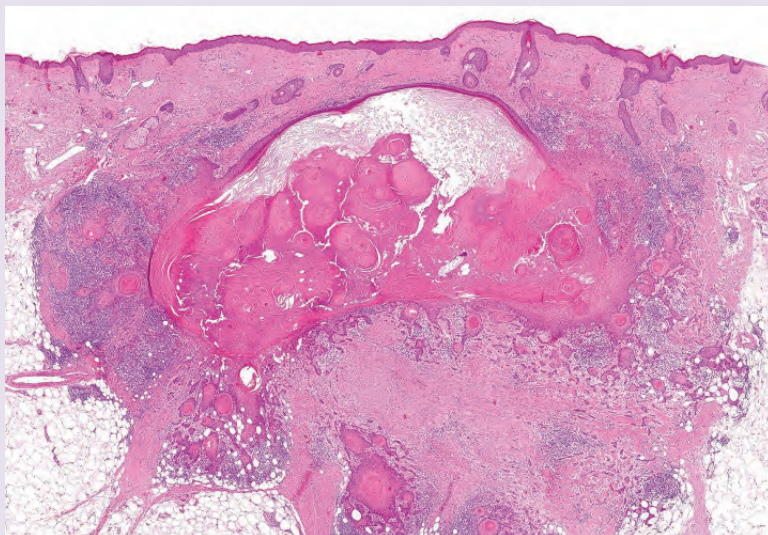
Myxoid tumor
differentiation
and tumor
stroma

Proliferation of
well
differentiated
tumor cells with
horn pearls

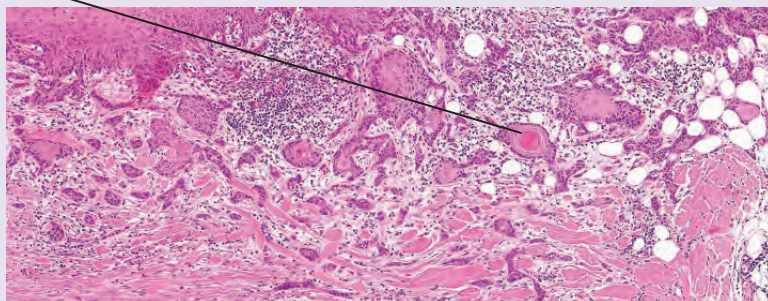
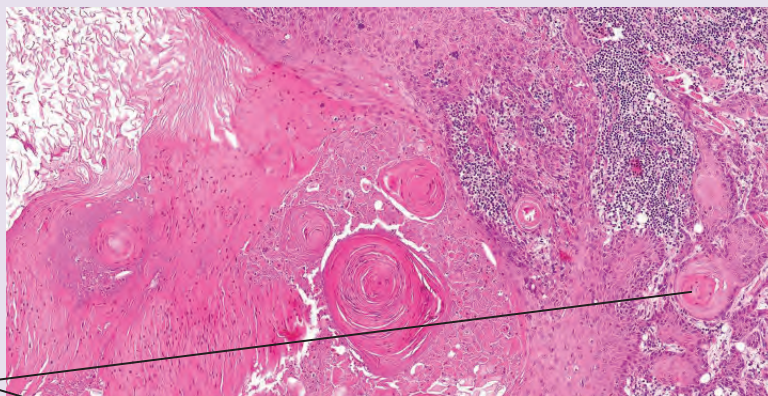


SQUAMOUS CELL CARCINOMA**Cl:** No specific clinical features.**Hi:** Myxoid fibrous stroma.**Variant: Follicular (Infundibular) SCC**

Association with
sebfollicular
structures



Formation of
pseudo-follicular
structures



SQUAMOUS CELL CARCINOMA

Some squamous cell carcinomas have follicular differentiation, arising from the infundibular portion of hair follicles. While they may overlap histologically with keratoacanthoma, clinically they are rarely confused with this entity.

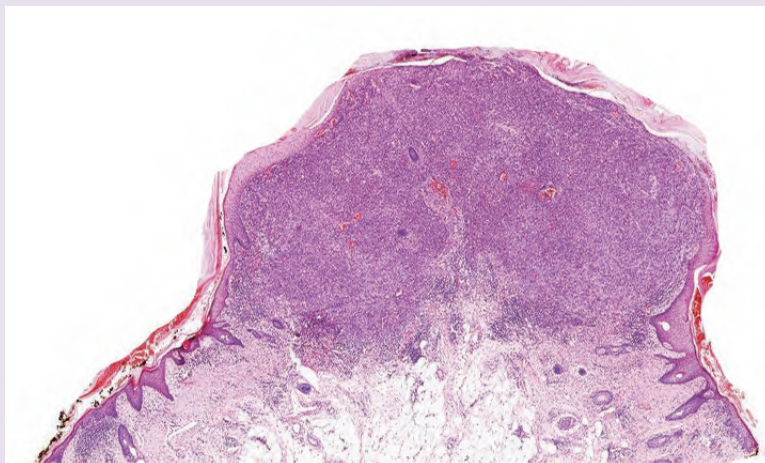
CI: Simulating keratoacanthoma.

Hi:

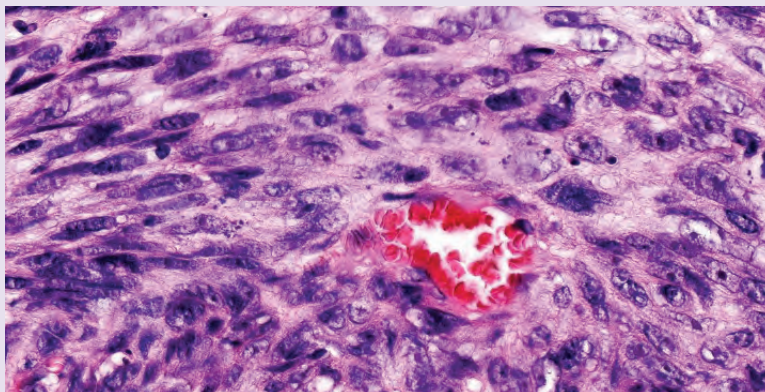
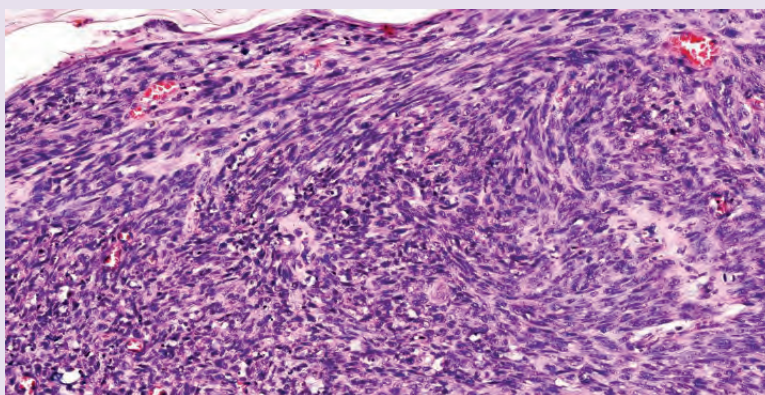
- Arising from the infundibular portion of the hair follicle
- Abortive follicular structures

Variant: Spindle Cell (Fuscellular) SCC

Exophytic
epithelial tumor
without
keratinization



Epithelial
spindle
cells



SQUAMOUS CELL CARCINOMA

This variant presents with a tumor pattern that must be immunohistochemically separated from other epithelial and mesenchymal spindle cell tumors.

Cl: No specific clinical features.

Hi: Differentiation from other spindle cell tumors, especially from amelanotic melanoma, must be based on immunohistochemistry. Malignant melanoma reliably expresses S100 and SOX10, and is always negative for pancytokeratin. Spindled SCCs are frequently positive for vimentin, further adding to the confusion with mesenchymal neoplasms.

DD: Malignant (amelanotic) melanoma.

Squamous Cell Carcinomas in Special Sites

Cl: SCCs on ear, lip, penis, vulva, and tongue often are misdiagnosed at incipient stages of tumor evolution and may be mistaken for infectious disorders. However, due to the loss of differentiation, tumors at these sites often show a progressive course and tend to metastasize into the local lymph nodes.

Squamous Cell Carcinomas in Special Sites

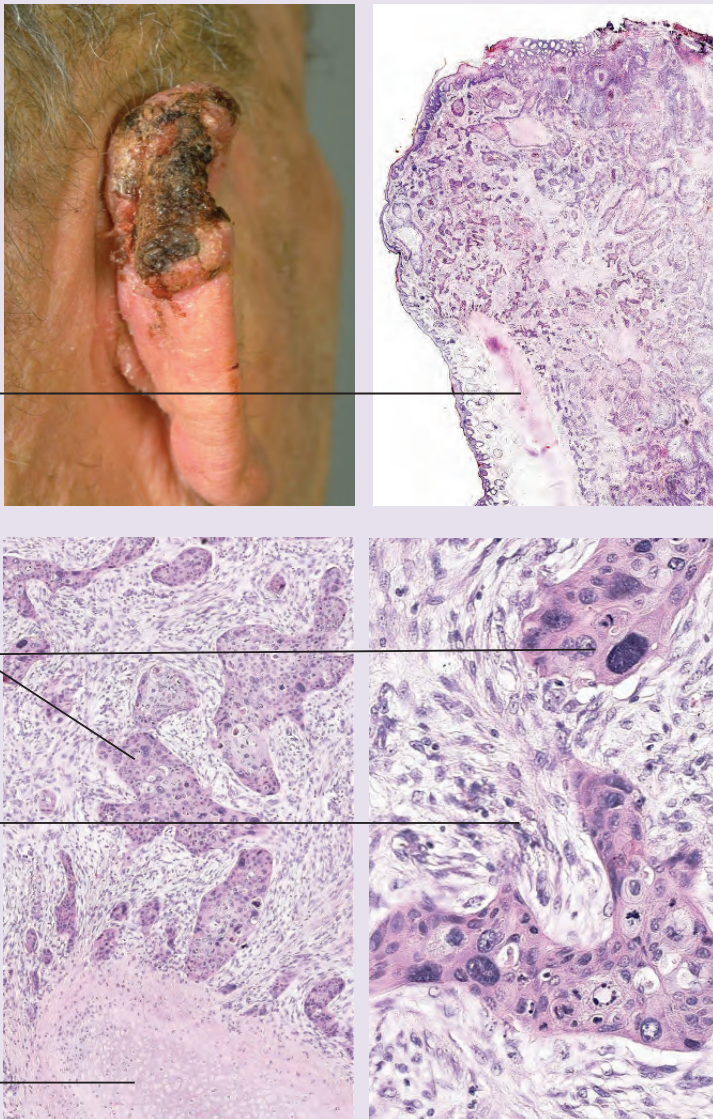
Ulcerated tumor of the ear concha, covered with crusts

Cartilage

Anaplastic tumor cells

Fibrous stroma

Cartilage



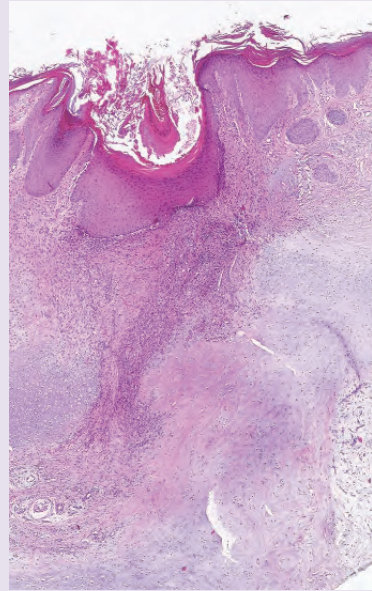
SQUAMOUS CELL CARCINOMA

Differential Diagnosis: Chondrodermatitis Nodularis Helicis of Winkler

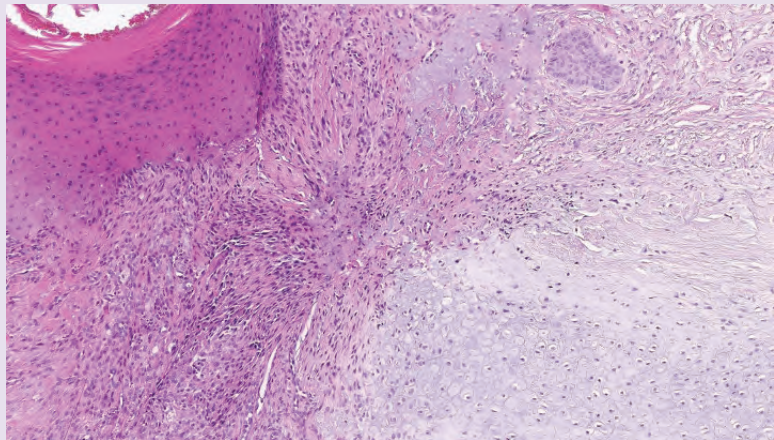
Crateriform lesion (left)



Endophytic crater with epidermal hyperplasia and adjacent granulation tissue, overlying eroded cartilage (right)



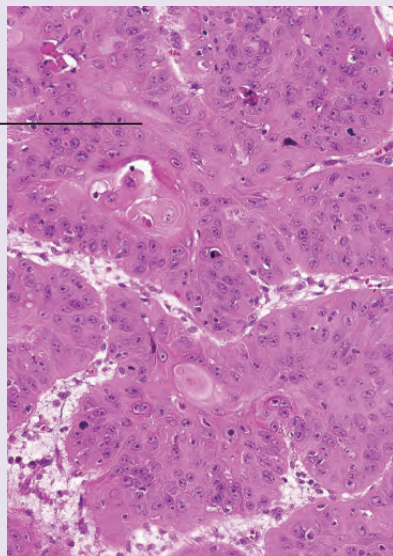
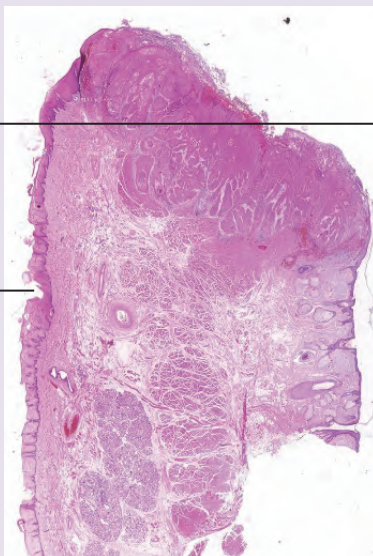
Epidermal hyperplasia, granulation tissue, eroded cartilage



SQUAMOUS CELL CARCINOMA**Special Sites: SCC of the Lip**

Carcinomatous
tumor cells with
moderate
differentiation

Inner, buccal
mucosa



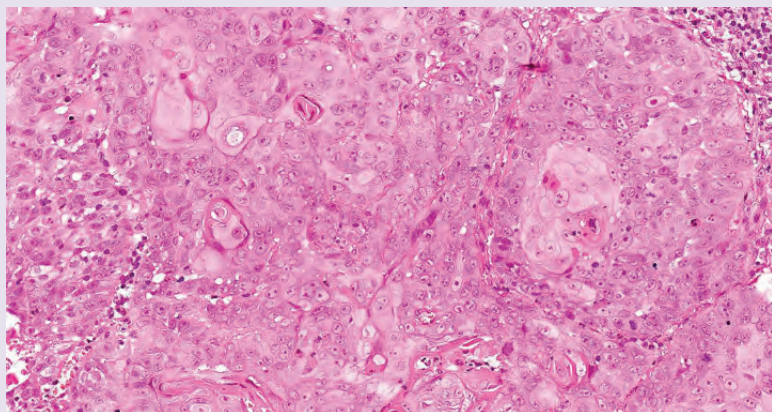
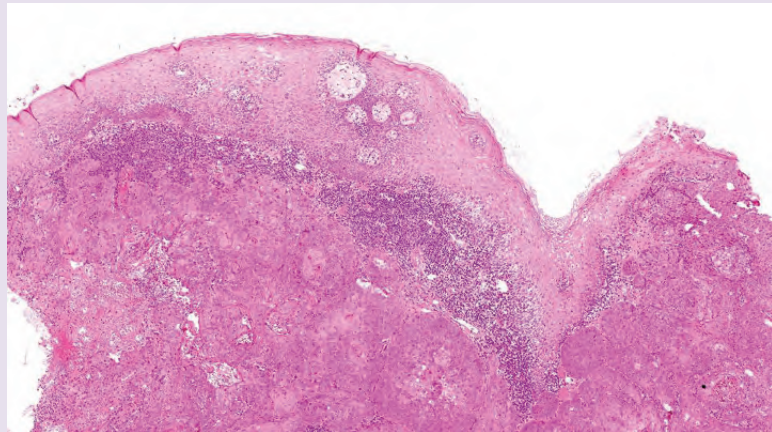
SQUAMOUS CELL CARCINOMA

Special Sites: SCC of the Tongue

Ulcerated SCC
of the tongue

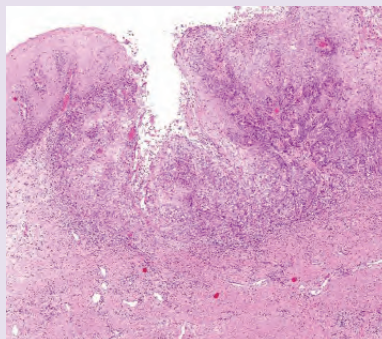


Invasive
carcinoma with
large, poorly
differentiated
squamous
epithelial cells

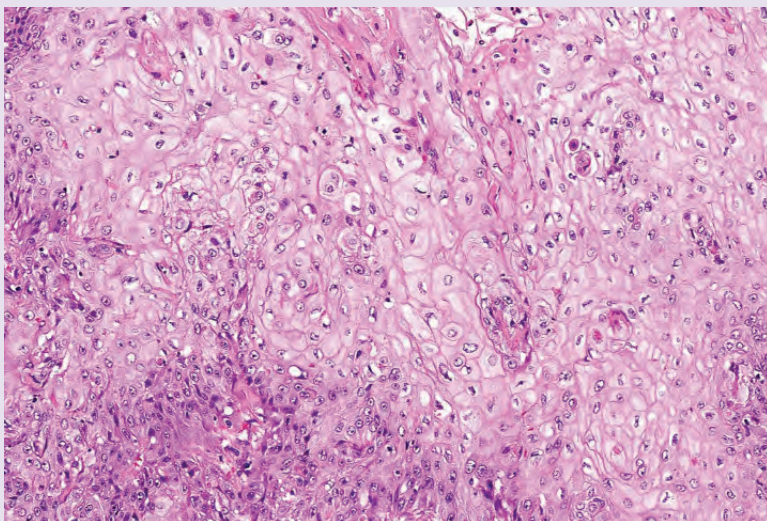


SQUAMOUS CELL CARCINOMA**Special Sites: SCC of the Penis**

Ulcerated tumor
of the glans
penis



Undifferentiated
large, pale tumor
cells

**Hi:**

- Often ulcerated
- Undifferentiated cytomorphology with minimal keratinization
- Highly atypical, pale anaplastic epithelial tumor cells

- Many mitoses

- Inflammatory infiltrate, containing many plasma cells

DD (ear): Chondrodermatitis nodularis helices of Winkler.

CHAPTER 2

Adnexal

CHAPTER MENU

Sweat Gland Differentiation	Malignant Neoplasms
Nevi, Hyperplasias, and Benign Adnexal	Hair Follicle Differentiation
Neoplasms (BAN)	Nevi, Hyperplasia, and Hamartomas
Malignant Adnexal Neoplasms	Benign Neoplasms
Sebacaceous Differentiation	Malignant Neoplasms
Hyperplasias and Hamartomas	Pilosebaceous Mesenchyme
Benign Neoplasms	Benign Neoplasm

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Sweat Gland Differentiation

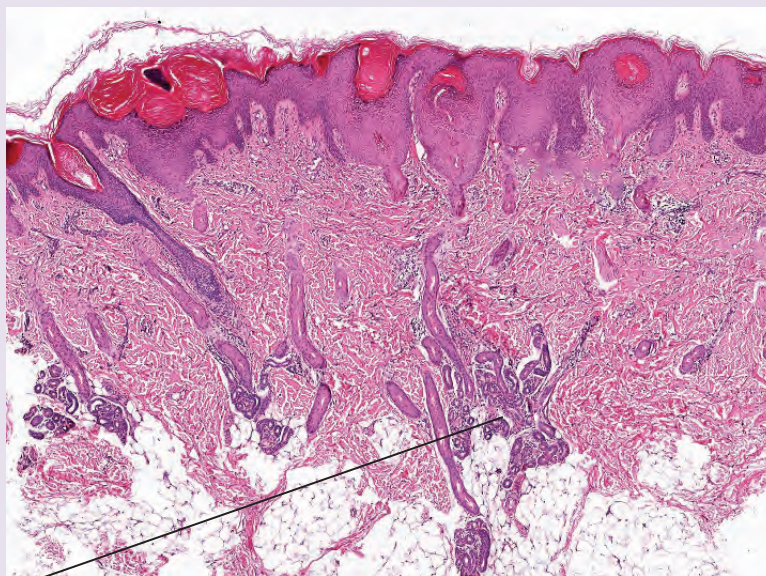
A clearcut differentiation between the preferential origin (eccrine or apocrine) of an adnexal neoplasm is often not possible, since both structural elements may be seen side by side in the

same lesion. However, elongated ductal structures are a clue to an apocrine origin of the lesion.

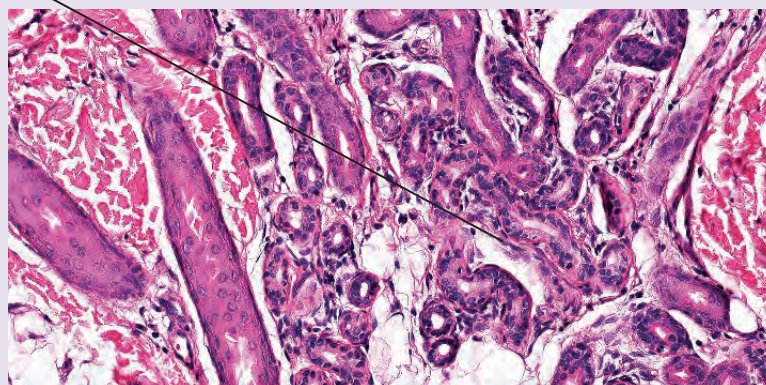
Nevi, Hyperplasias, and Benign Adnexal Neoplasms (BAN) Eccrine Differentiation

Sweat Gland Nevus

Acanthosis,
hyperkeratosis,
multiple sweat
ducts



Clusters of
enlarged coiled
eccrine sweat
glands



Cl: Plaque with localized hyperhidrosis. Very rare.

Hi:

- Densely packed clusters of normal or enlarged eccrine sweat glands, sometimes embedded in mucinous stroma
- Acanthosis and hyperkeratosis

DD: Epidermal nevus with eccrine differentiation.

References

- Frouin, E., Riviere, B., Maillet, O., et al. (2016) Coccygeal polypoid eccrine nevus associated with imperforate anus and unilateral multicystic kidney dysplasia. *J Cutan Pathol* **43**(8): 697–701.
- Luo, D.Q., Huang, C.Z., Xie, W.L., Xu, F.F., and Mo, L.Q. (2015) Hybrid eccrine gland and hair follicle

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

hamartoma: a new entity of adnexal nevus. *Am J Dermatopathol* **37**(2): 167–70.

Martorell-Calatayud, A., Colmenero, I., Hernandez-Martin, A., Requena, L., and Torrelo, A. (2010) Porokeratotic eccrine and hair follicle nevus. *Am J Dermatopathol* **32**(5): 529–30.

Shaffer, H.C., Schosser, R., and Phillips, C. (2009) Acantholytic dyskeratotic epidermal nevus with eccrine differentiation: a case report and review of literature. *J Cutan Pathol* **36**(9): 1001–4.

Eccrine Syringofibroadenoma (Mascaro Tumor)

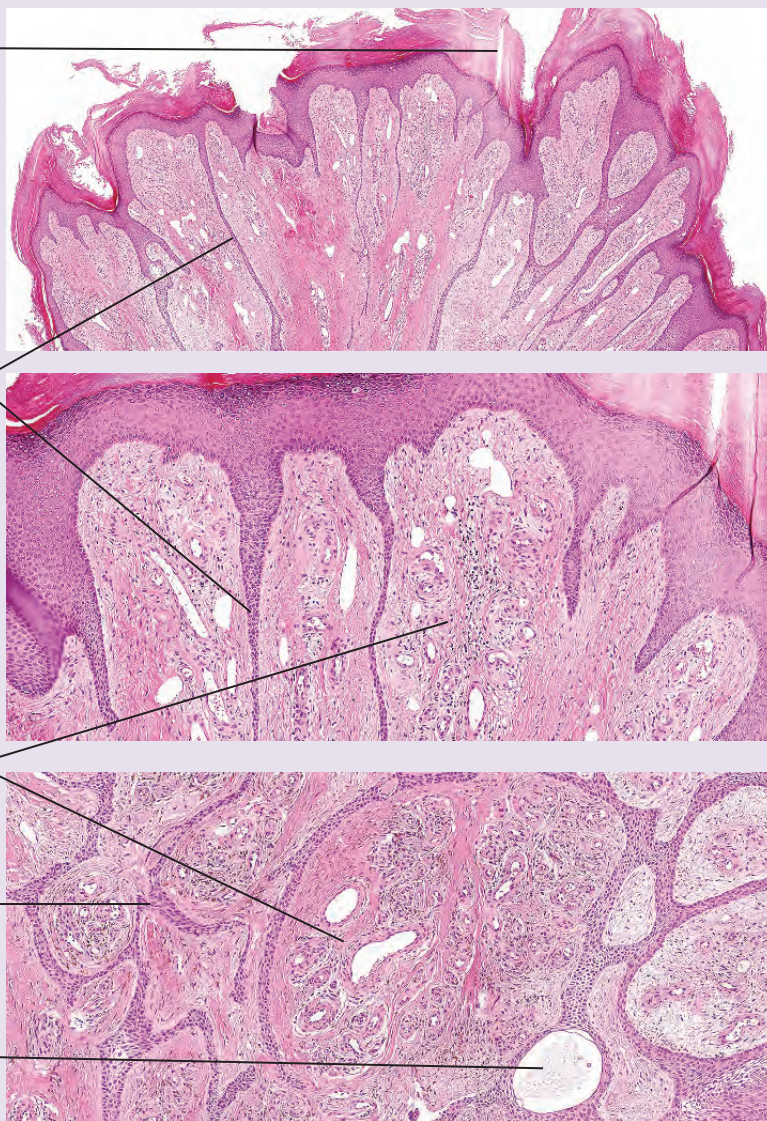
Hyperkeratosis

Elongated
ductal
epithelial
strands

Richly
vascularized
stroma with
capillaries
and venules

Anastomosing
epithelial
(ductal)
strands

Dilated duct



Cl: Rare solitary, hyperkeratotic tumor, preferentially on the extremities. The tumor presents with a “tapioca pudding”-like surface. Considered to be a reactive change within chronic irritated skin; also designated as acrosyringial nevus.

Hi:

- Acanthosis with moderate hyperkeratosis
- Elongated rete ridges
- Small ductal structures within the epithelial strands
- Richly vascularized stroma

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

DD: Fibroepithelioma of Pinkus; reticulate seboreithic keratosis; eccrine poroma.

References

- Cota, C., Ferrara, G., Amantea, A., and Donati, P. (2011) Eccrine syringofibroadenoma and clear cell acanthoma: an association by chance? *Am J Dermatopathol* **33**(2): 195–8.
- Shalin, S.C., Rinaldi, C., and Horn, T.D. (2013) Clear cell acanthoma with changes of eccrine syringofibroade-

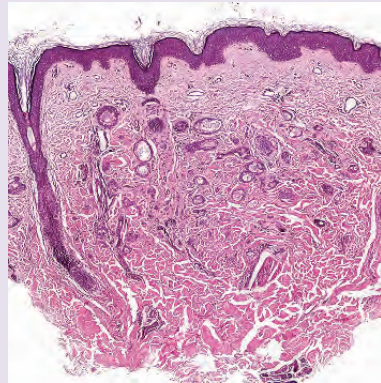
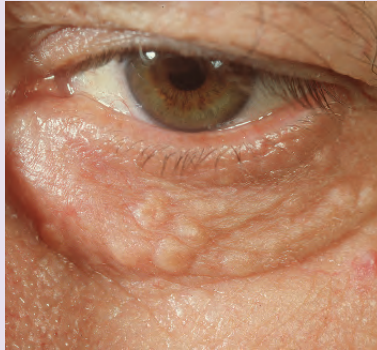
noma: reactive change or clue to etiology? *J Cutan Pathol* **40**(12): 1021–6.

- Tan, T., Guitart, J., Liu, L.L., et al. (2017) Eccrine syringofibroadenoma in association with acquired epidermodysplasia verruciformis. *Am J Dermatopathol* **39**(7): 534–7.
- Weedon, D. and Lewis, J. (1977) Acrosyringal nevus. *J Cutan Pathol* **4**(3): 166–8.

Syringoma (Eruptive Hidradenoma)

Flat papules (left)

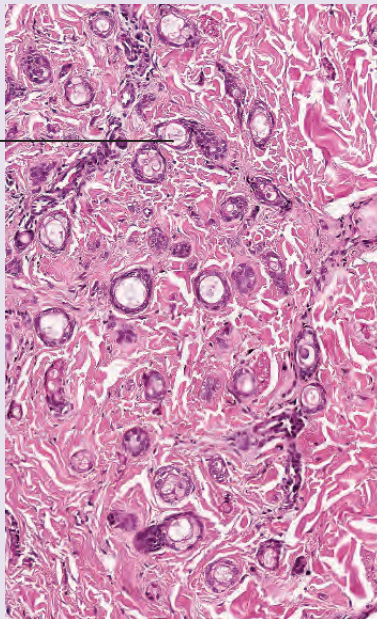
Accumulation of cystic and ductal structures in the upper and mid dermis (right)



Cysts and short ducts ("tadpoles")

Fibrotic stroma

Two layers of epithelial cells, surrounding (PAS-positive) amorphous material (right)



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Most common, especially in young women, in the periorbital region but also occurs in other locations (vulva) in association with eccrine glands. Multiple tiny, smooth skin-colored or yellowish intradermal papules.

Hi:

- Involvement of the upper dermis
- Tiny tennis racket-like cystic and ductal structures (“tadpoles”)
- Double layer of epithelial cells
- Fibrotic stroma
- PAS-positive clear cell variants (rare)

References

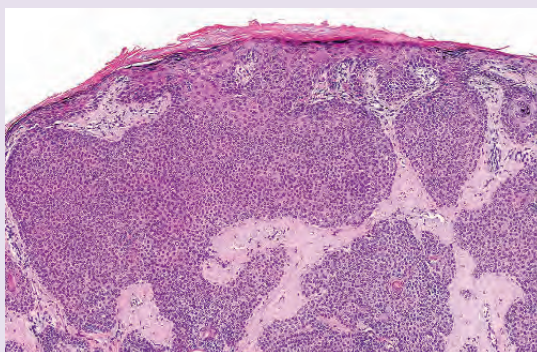
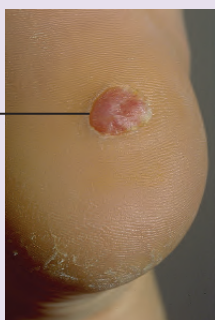
- Alonso-Riano, M., Camara-Jurado, M., Garrido, M.C., and Rodriguez-Peralto, J.L. (2015) Papular clear cell hyperplasia of the eccrine duct: a precursor lesion of clear cell syringoma? *Am J Dermatopathol* **37**(9): 701–3.
- Incel Uysal, P., Yalcin, B., Ozhamam, E., and Bozdogan, O. (2017) Coexistence of adult onset eruptive syringoma and bilateral renal cell carcinoma: a case report. *Am J Dermatopathol* **39**(1): 56–8.

Poroma

Three variants can be differentiated: common solid poroma, hidroacanthoma simplex, and dermal duct tumor.

Variant: Common Solid Poroma

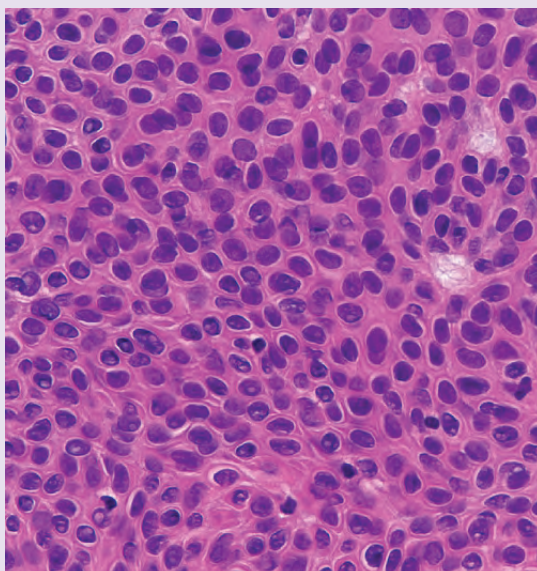
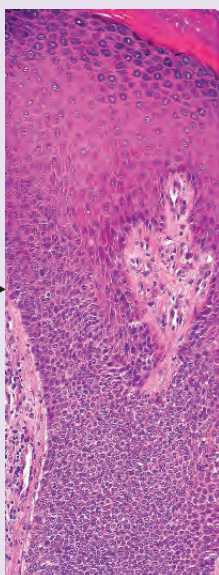
Red tumor delineated by a lip-like epidermal collerette



Solid islands of poroid cells, showing broad connection with the epidermis

Sharp demarcation

Small poroid cells and larger pale cuticular cells (right)



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Protuberant eroded painful (on pressure) benign, usually solitary, sharply circumscribed sweat gland tumor, preferentially on the foot. Multiple lesions may occur. Malignant poromas (porocarcinomas) are rare.

Hi:

- Solid invasive basaloid tumor, containing two morphologically different epithelial cell types:

- Small poroid cells with eosinophilic basaloid roundish morphology
- Larger, pale cuticular cells corresponding to the inner layer of sweat ducts

- Marked focal necrosis (“necrosis en masse”)

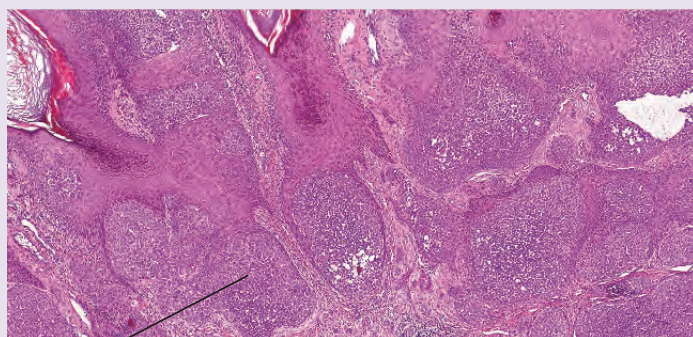
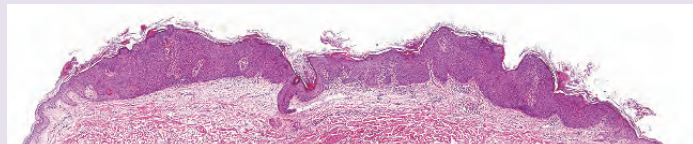
DD: Eccrine acrospiroma; basal cell carcinoma; trichilemmoma.

Variant: Hidroacanthoma simplex

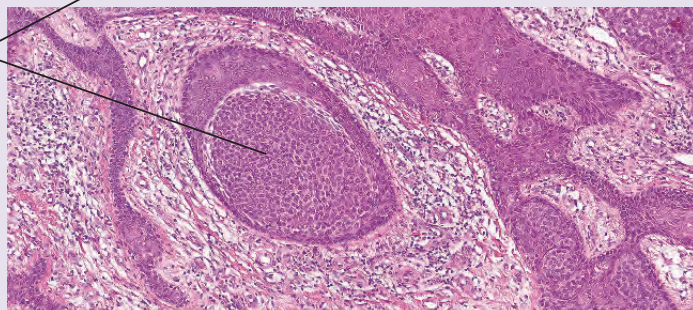
Lesion on the lower leg



Flat acanthosis



Intraepidermal nests of poroid cells sharply demarcated from surrounding keratinocytes



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Circumscribed flat, brown, sometimes hyperkeratotic lesion, resembling flat seborrheic keratosis.

Hi:

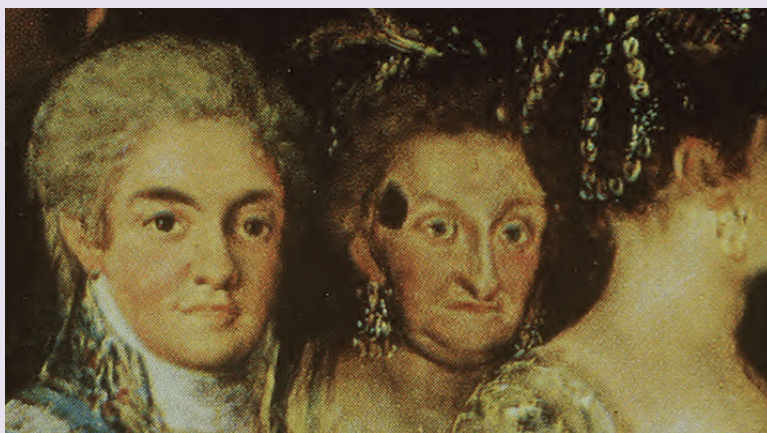
- Acanthotic epidermis
- Clonal intraepidermal nests of poroid cells

- Prominent peripheral basaloid rimming by sharply demarcated regular keratinocytes

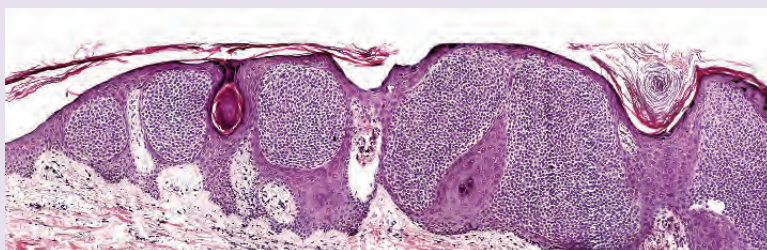
DD: Seborrheic keratosis with intraepidermal clonal proliferation (intraepidermal epithelioma of Borst–Jadassohn). Seborrheic keratoses do not appear on palms or soles.

Differential Diagnosis: Intraepidermal Epithelioma of Borst–Jadassohn (Seborrheic Keratosis)

Francisco de Goya:
Karl IV. and
his family
(Prado, Madrid).
Detail showing
flat seborrheic
keratosis on
the right temple



Intraepidermal
clones of
basaloid
epidermal cells,
surrounded by
normal
keratinocytes
(mid and
bottom)



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

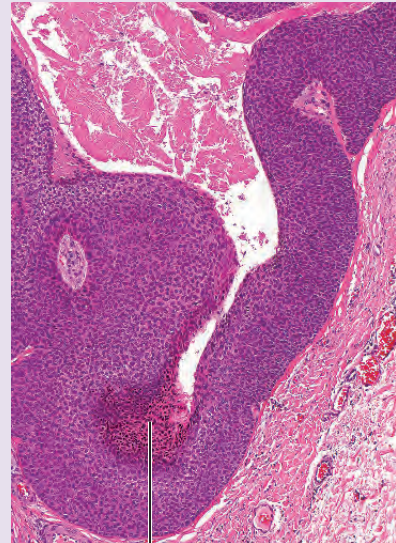
Cl: Usually flat seborrheic keratosis, which does not occur on the planta or palma.

Hi: Acanthosis of the epidermis showing clonal nests of basaloid epidermal cells surrounded by

regular keratinocytes. Nests are composed of irregularly arranged keratinocytes lacking cytological atypia.

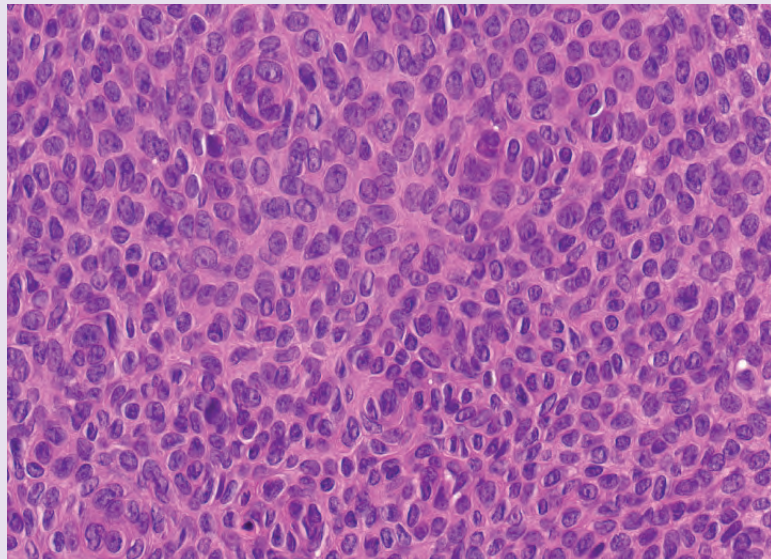
Variant: Dermal duct tumor

Cyst
Poroid cells, no connection with the epidermis (left and right)



Typical "necrosis en masse"

Poroid cells with pink cytoplasm

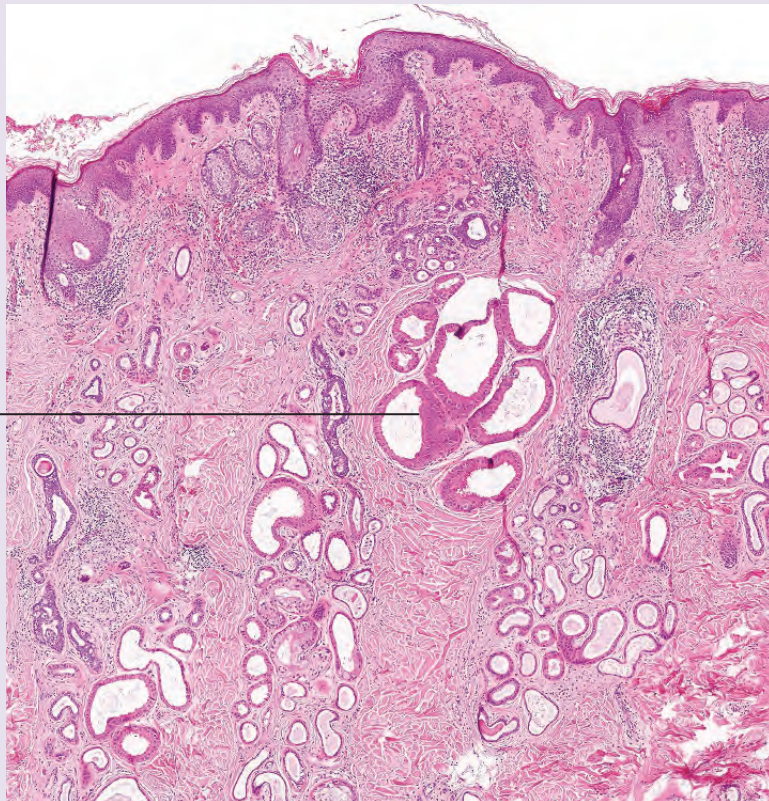


Cl: Inconspicuous papulonodular lesion.

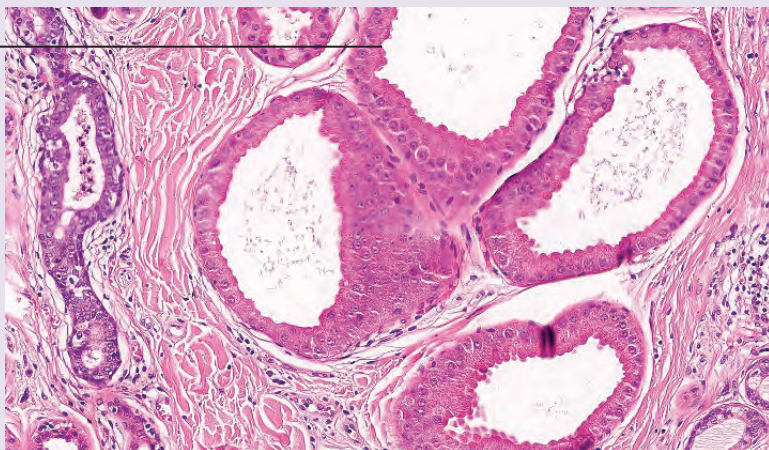
Hi: No (broad) connection with the epidermis.

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS**Apocrine Differentiation****Apocrine Nevus**

Apocrine
sweat glands



Decapitation
secretion



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Apocrine nevi are very rare and have no distinct clinical appearance.

Hi:

- Apocrine sweat gland structures
- Decapitation secretion
- Frequent association with proliferation of hair follicles or sebaceous glands

References

Ando, K., Hashikawa, Y., Nakashima, M., Nakayama, A., and Ohashi, M. (1991) Pure apocrine nevus. A study of

light-microscopic and immunohistochemical features of a rare tumor. *Am J Dermatopathol* **13**(1): 71–6.

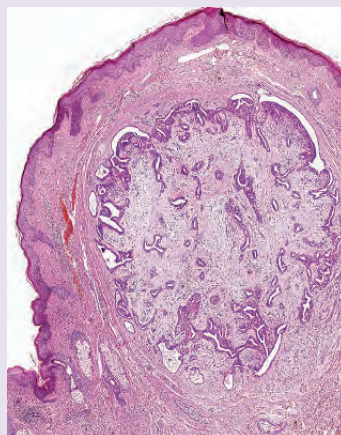
Cordero, S.C., Royer, M.C., Rush, W.L., Hallman, J.R., and Lupton, G.P. (2012) Pure apocrine nevus: a report of 4 cases. *Am J Dermatopathol* **34**(3): 305–9.

Kim, J.H., Hur, H., Lee, C.W., and Kim, Y.T. (1988) Apocrine nevus. *J Am Acad Dermatol* **18**(3): 579–81.

Neill, J.S. and Park, H.K. (1993) Apocrine nevus: light microscopic, immunohistochemical and ultrastructural studies of a case. *J Cutan Pathol* **20**(1): 79–83.

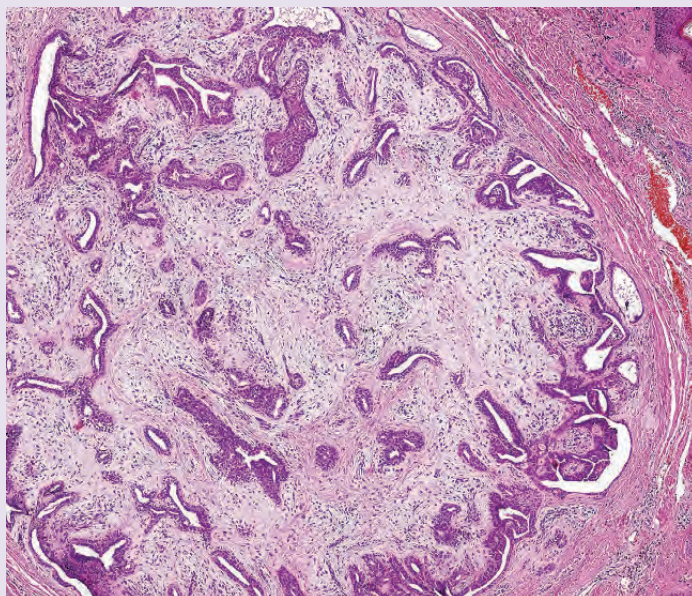
Mixed Tumor of the Skin (Chondroid Syringoma)

Nodule on the neck



Peritumoral cleft formation (top and below)

Branching tubular ducts within a mucinous stroma



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Small firm cutaneous or subcutaneous nodules, mostly located in the head and neck area. Usually benign, also considered to be a morphological variant of cutaneous myoepithelioma. Malignant mixed tumors of the skin exist.

Hi:

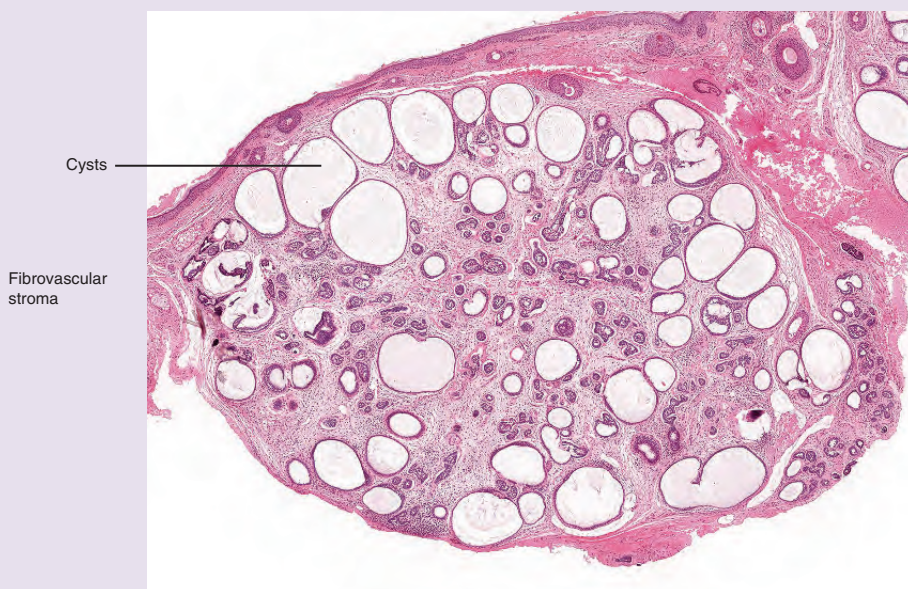
- Roundish sharply circumscribed tumor
- “Mixed” variety of structures: eccrine, apocrine, sebaceous, pilar, mucinous
- Branching tubules and clusters of epithelial cells with eccrine, apocrine, sebaceous or pilar differentiation
- All structures embedded in mucinous stroma
- Islands of chondroid (cartilage) differentiation and metaplastic ossification, especially in apocrine variant
- Clusters of large “plasmacytoid” epithelial cells (myoepithelial) with co-expression of S100 and alpha smooth muscle actin

- Eccrine variants present with a prominent chondroid stroma and embedded monomorphic tubular strands that strongly express S100

References

- Headington, J.T. (1961) Mixed tumors of skin: eccrine and apocrine types. *Arch Dermatol* **84**: 989–96.
- Jun, H.J., Cho, E., Cho, S.H., and Lee, J.D. (2012) Chondroid syringoma with marked calcification. *Am J Dermatopathol* **34**(8): e125–7.
- Nguyen, C.M. and Cassarino, D.S. (2017) Local recurrence of cutaneous mixed tumor (chondroid syringoma) as malignant mixed tumor of the thumb 20 years after initial diagnosis. *J Cutan Pathol* **44**(3): 292–5.
- Requena, C., Brotons, S., Sanmartin, O., et al. (2013) Malignant chondroid syringoma of the face with bone invasion. *Am J Dermatopathol* **35**(3): 395–8.

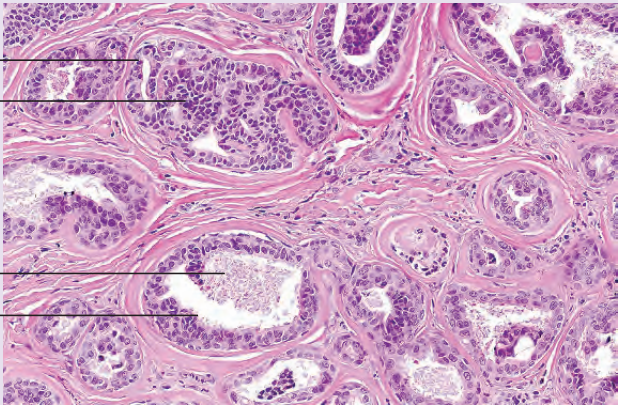
Tubular Adenomas: Papillary “Eccrine” (Misnomer) and Tubular Apocrine Adenoma



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Tubular Adenomas: Papillary “Eccrine” (Misnomer) and Tubular Apocrine Adenoma

Two layers of cuboidal cells
Papillary projections
Eosinophilic debris
Apocrine secretion

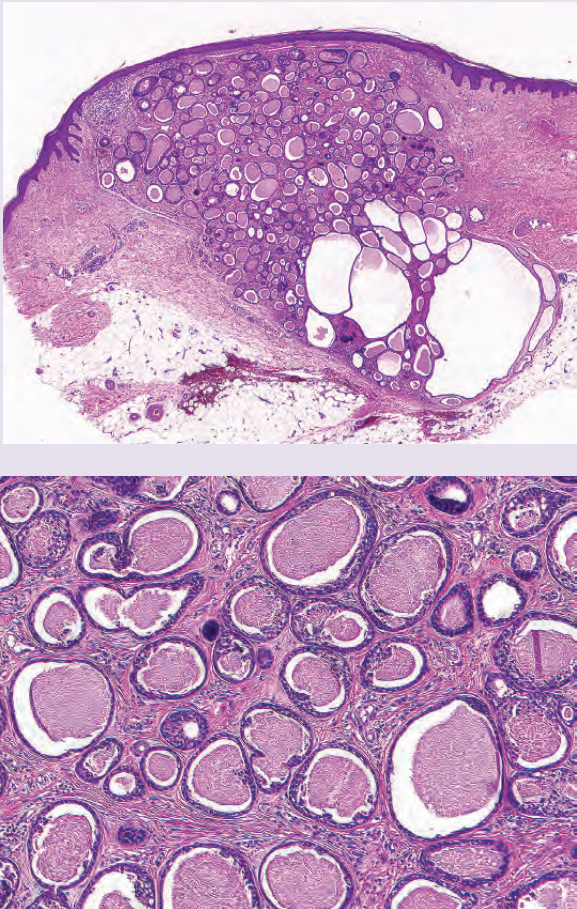


This histological image displays a cross-section of skin with several tubular adenomas. The structures are characterized by two layers of cuboidal cells forming papillary projections into the lumen. The lumens contain eosinophilic debris and apocrine secretions. The surrounding stroma is fibrous and contains some inflammatory cells.

Tubular Adenomas: Papillary “Eccrine” (Misnomer) and Tubular Apocrine Adenoma

Dermal tumor with tubular and cystic components

Ductal structures with double-layered cyst wall. Apocrine secretion and eosinophilic debris



The top image is a low-power view of a dermal tumor with tubular and cystic components. The tumor is located in the dermis and is composed of numerous tubular and cystic structures. The bottom image is a high-power view of ductal structures with double-layered cyst walls. The lumens of these ducts contain apocrine secretions and eosinophilic debris.

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Apocrine tubular adenoma and eccrine papillary adenoma are closely related and differ mainly by localisation and predominant type of secretion. The presence of ducts is a clue to apocrine origin.

Cl: Well-circumscribed intradermal papule with preferential localisation on the extremities or scalp.

Hi:

- Intradermal tumor, consisting of small tubular strands and cysts, embedded in fibrous stroma
- The ductal epithelium has two layers of cuboidal cells
- Small intraluminal papillary projections (pseudopapillae)
- Signs of apocrine secretion (“epithelial snouts”) may be present
- Minimal necrosis
- No mitotic activity

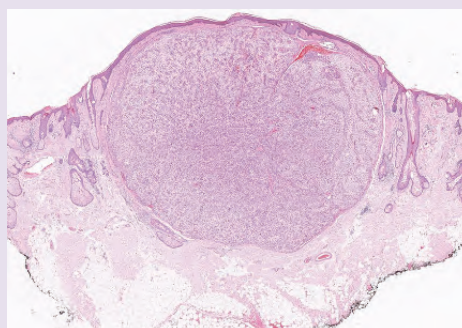
References

- Ansai, S.I., Anan, T., Fukumoto, T., and Saeki, H. (2016) Tubulopapillary cystic adenoma with apocrine differentiation: a unifying concept for syringocystadenoma papilliferum, apocrine gland cyst, and tubular papillary adenoma. *Am J Dermatopathol* **39**(11): 829–37.
- Ito, T., Nomura, T., Fujita, Y., Abe, R., and Shimizu, H. (2014) Tubular apocrine adenoma clinically and dermoscopically mimicking basal cell carcinoma. *J Am Acad Dermatol* **71**(2): e45–6.
- Kazakov, D.V., Bisceglia, M., Calonje, E., et al. (2007) Tubular adenoma and syringocystadenoma papilliferum: a reappraisal of their relationship. An interobserver study of a series, by a panel of dermatopathologists. *Am J Dermatopathol* **29**(3): 256–63.
- Kazakov, D.V., Mukensnabl, P., and Michal, M. (2006) Tubular adenoma of the skin with follicular and sebaceous differentiation: a report of two cases. *Am J Dermatopathol* **28**(2): 142–6.
- Montalli, V.A., Martinez, E., Tincani, A., et al. (2014) Tubular variant of basal cell adenoma shares immunophenotypical features with normal intercalated ducts and is closely related to intercalated duct lesions of salivary gland. *Histopathology* **64**(6): 880–9.

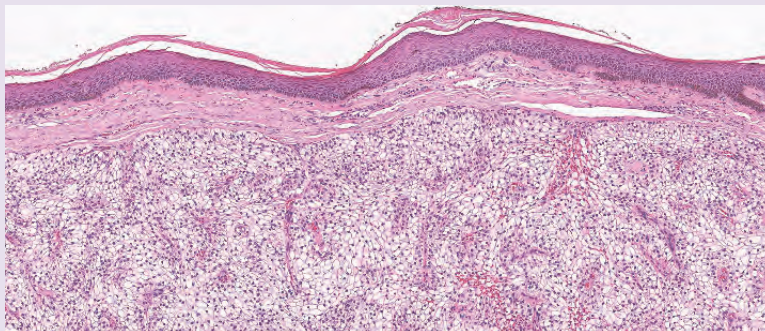
“Eccrine” (misnomer) Acrospiroma (Nodular Clear Cell Hidradenoma, Solid Cystic Hidradenoma)

Dermal nodule on the scalp (left)

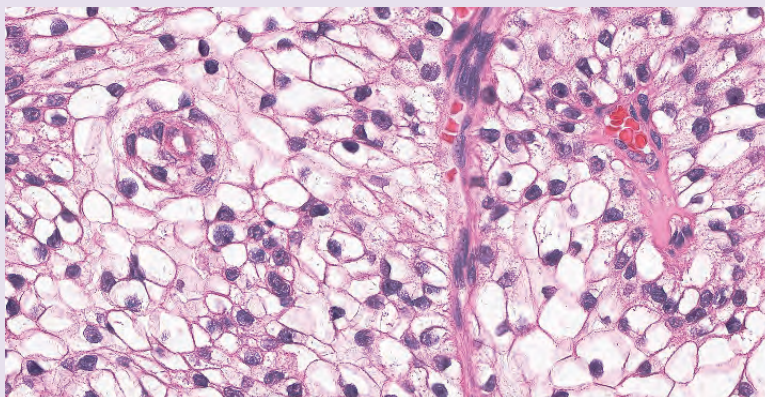
Well circumscribed dermal nodule (right)



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

“Eccrine” (misnomer) Acrospiroma (Nodular Clear Cell Hidradenoma, Solid Cystic Hidradenoma)

Pale (clear) tumor cells (mid and bottom)



Cl: Nodular tumor with smooth surface that may occur at any localisation and at any age,

Hi:

- Well-circumscribed dermal tumor
- Aggregates of confluent epithelial lobules
- Characteristic feature: sclerotic tumor stroma between tumor nests
- Tumor cells with alternating morphology: pale clear cells and smaller cells with eosinophilic cytoplasm
- Minimal amounts of squamous differentiation
- Cystic and tubular structures may be focally present
- Low mitotic activity
- Transition to incipient malignancy may occur only focally (step sections!) with crowded nuclei (hyperchromasia), pleomorphism, increased mitotic activity

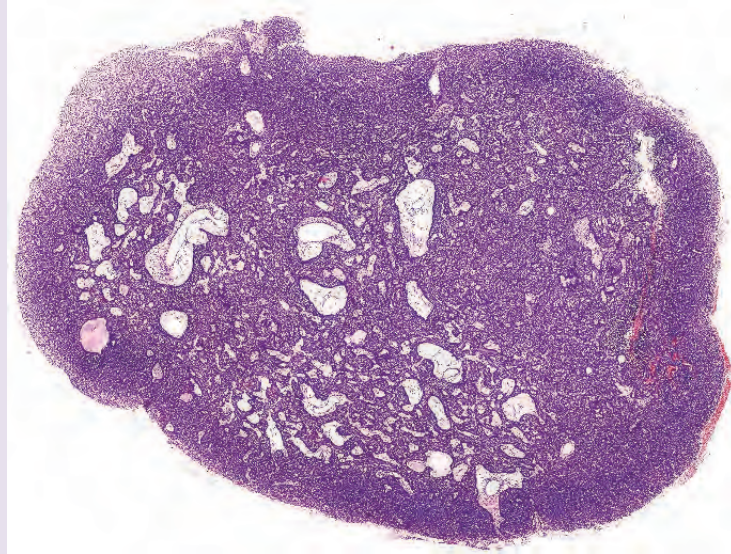
References

- Ahmed, A., Kim, W., and Speiser, J. (2017) Mucinous hidradenoma in a child: a case report and review of the literature. *J Cutan Pathol* Apr 21. doi: 10.1111/cup.12957 [epub ahead of print].
- Nandeesh, B.N. and Rajalakshmi, T. (2012) A study of histopathologic spectrum of nodular hidradenoma. *Am J Dermatopathol* **34**(5): 461–70.
- Tingaud, C., Costes, V., Frouin, E., et al. (2016) Lymph node location of a clear cell hidradenoma: report of a patient and review of literature. *J Cutan Pathol* **43**(8): 702–6.
- Yu, G., Goodloe, S. Jr, D’Angelis, C.A., McGrath, B.E., and Chen, F. (2010) Giant clear cell hidradenoma of the knee. *J Cutan Pathol* **37**(9): e37–41.

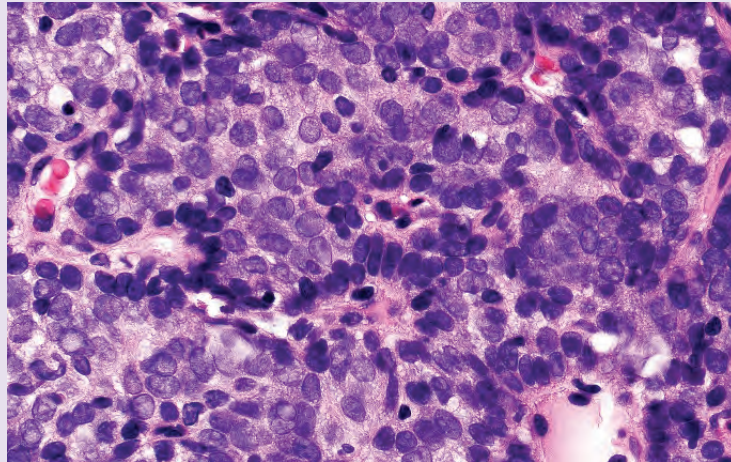
NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Spiradenoma

Well circumscribed nodule with tubular structures



Rosettes with small dark tumor cells in the periphery. Larger pale cells in the center.



Cl: Solitary or sometimes multiple grouped intradermal nodules in young adults with non-specific clinical appearance; mostly painful upon palpation. Frequent association with trichoepitheliomas and cylindromas suggests a genetic background. Apocrine and malignant variants (spiradenocarcinoma) exist.

Hi:

- Well-circumscribed nodule, may resemble lymph node in scanning magnification
- Two distinct cell populations of intermingled epithelial tumor cells (“pepper and salt” pattern):

- Small lymphocyte-like dark epithelial cells amidst
- Larger pale epithelial cells with vesicular nuclei
- Thick basement membrane (PAS) surrounding the tumor
- Ductal structures with PAS positivity
- There may be morphological overlap with cylindroma (thick basement membrane)

References

Ben Brahim, E., Sfia, M., Tangour, M., Makhoul, R., Cribier, B., and Chatti, S. (2010) Malignant eccrine spiradenoma: a new case report. *J Cutan Pathol* 37(4): 478–81.

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Kaku, Y., Fukumoto, T., and Kimura, T. (2015) Spiradenocarcinoma in preexisting spiradenoma with a large in situ adenocarcinoma component. *Am J Dermatopathol* **37**(10): e122–5.

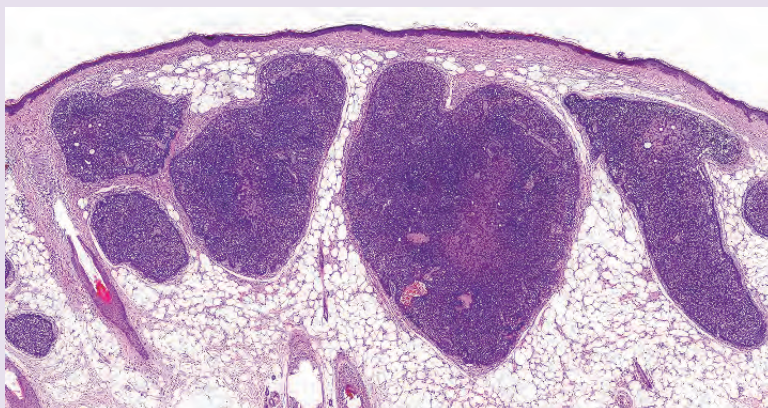
Sellheyer, K. (2015) Spiradenoma and cylindroma originate from the hair follicle bulge and not from the eccrine sweat gland: an immunohistochemical study with CD200 and other stem cell markers. *J Cutan Pathol* **42**(2): 90–101.

Cylindroma (Turban Tumor)

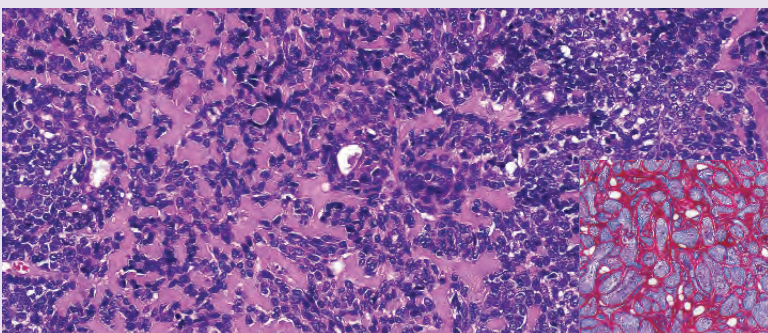
Multiple soft tumors on the head



Dermal tumor, resembling a jigsaw puzzle



Tumor nests surrounded by PAS- and collagen IV (inset) positive hyaline sheaths



CI: This autosomal inherited tumor occurs in childhood and usually presents as multiple, slowly growing, hairless soft nodules preferentially on the scalp. Morphological relationship to

eccrine spiradenoma and trichoepithelioma. There is some evidence that cylindroma and spiradenoma may originate from the follicular bulge rather than from eccrine sweat glands.

NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS**Hi:**

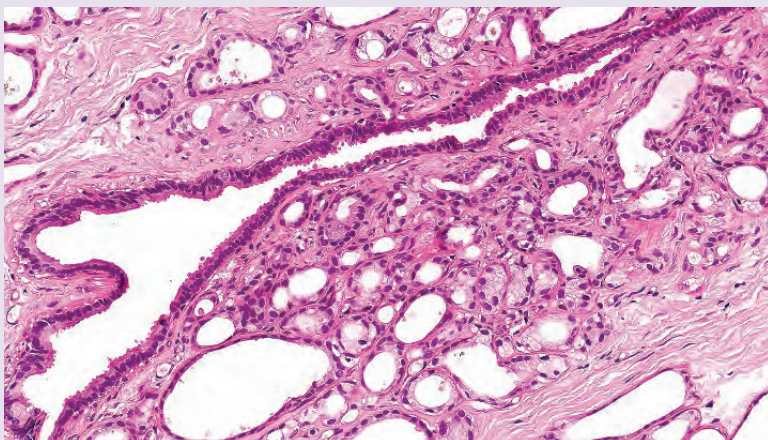
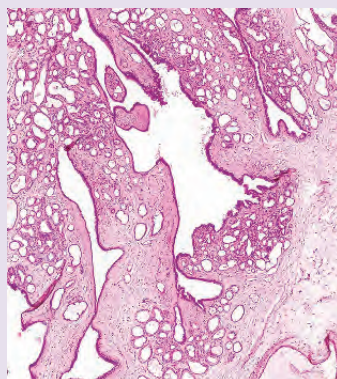
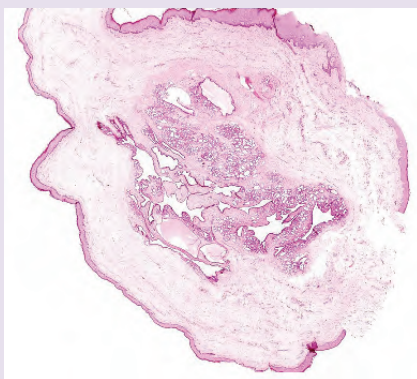
- Multiple islands of tumor cells arranged in a dense, jigsaw puzzle-like pattern
- Tumor nests are surrounded by PAS-positive hyaline sheaths
- The predominant tumor cell shows a roundish basaloid morphology with a small vesicular nucleus
- Tiny tubular structures may be present
- Malignant variants exist

References

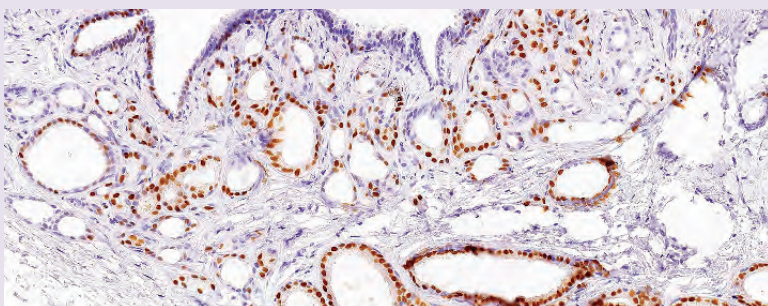
- Donner, L.R. (2012) Well-differentiated malignant cylindroma. *Am J Dermatopathol* **34**(6): 677.
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Anogenital Mammary-Like Gland

Polyp with mammary-like glandular structures (top and mid)



Estrogen receptor staining of apocrine secretory cells



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Polypous lesion in the anogenital area, originating from apocrine glands. Tumor evolution into extramammary Paget's disease may occur.

Hi: Aggregates of ectopic mammary gland structures in the dermis, surrounded by a fibrous stromal reaction.

References

- Charfi, S., Sevestre, H., Dumont, F., Regimbeau, J.M., and Chatelain, D. (2009) Atypical apocrine proliferation involving anogenital mammary-like glands of the perianal region. *J Cutan Pathol* **36**(Suppl 1): 52–5.
- Kazakov, D.V., Bisceglia, M., Sima, R., and Michal, M. (2006) Adenosis tumor of anogenital mammary-like glands: a case report and demonstration of clonality by HUMARA assay. *J Cutan Pathol* **33**(1): 43–6.
- Kazakov, D.V., Hugel, H., Vanecek, T., and Michal, M. (2006) Unusual hyperplasia of anogenital mammary-like glands. *Am J Dermatopathol* **28**(2): 134–7.
- Konstantinova, A.M., Kyrpychova, L., Belousova, I.E., et al. (2017) Anogenital mammary-like glands: a study of their normal histology with emphasis on glandular depth, presence of columnar epithelial cells, and distribution of elastic fibers. *Am J Dermatopathol* **39**(9): 663–667.
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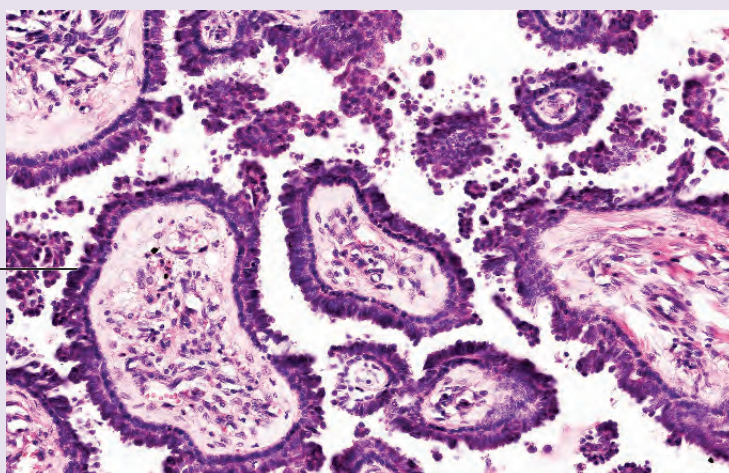
Hidradenoma Papilliferum (Apocrine Papillary Cystadenoma)

Cystic lesion with intraluminal papillary projections (papillae and pseudo-papillae)



Decapitation secretion

Fibrovascular stroma



NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Cl: Typically located in the genital region (labia) of young women; rarely in other locations (chest).

Hi:

- Cystic lesion with sharp circumscription and anastomosing lacunae and cystic spaces
- No connection with the overlying epidermis
- Focal epithelial intraluminal papillae
- Double layer of cuboidal epithelial cells with apocrine secretion (inner layer) and myoepithelial immunophenotype (outer layer)
- Decapitation secretion throughout the entire tumor

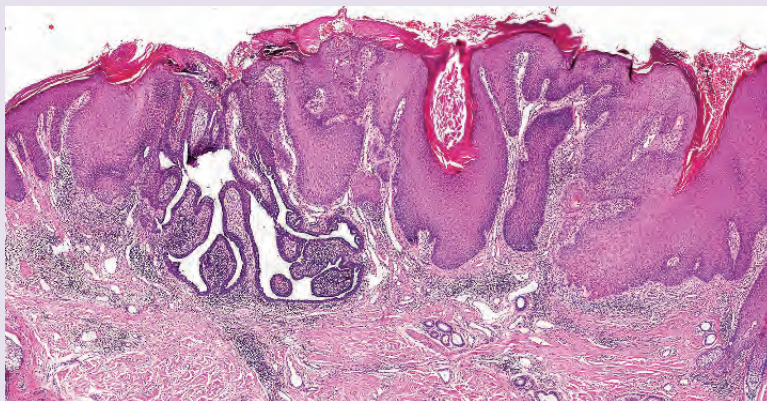
DD: Syringocystadenoma papilliferum; anogenital mammary-like glands.

References

- Elbendary, A., Cochran, E., Xie, Q., et al. (2016) Hidradenoma papilliferum with oncocytic metaplasia: a histopathological and immunohistochemical study. *Am J Dermatopathol* **38**(6): 444–7.
- El-Khoury, J., Renald, M.H., Plantier, F., Avril, M.F., and Moyal-Barracco, M. (2016) Vulvar hidradenoma papilliferum (HP) is located on the sites of mammary-like anogenital glands (MLAGs): analysis of the photographs of 52 tumors. *J Am Acad Dermatol* **75**(2): 380–4.
- Fernandez-Acenero, M.J., Sanchez, T.A., Sanchez, M.C., and Requena, L. (2003) Ectopic hidradenoma papilliferum: a case report and literature review. *Am J Dermatopathol* **25**(2): 176–8.
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- Tanaka, M., and Shimizu, S. (2003) Hidradenoma papilliferum occurring on the chest of a man. *J Am Acad Dermatol* **48**(2 Suppl): S20–1.

Syringocystadenoma Papilliferum

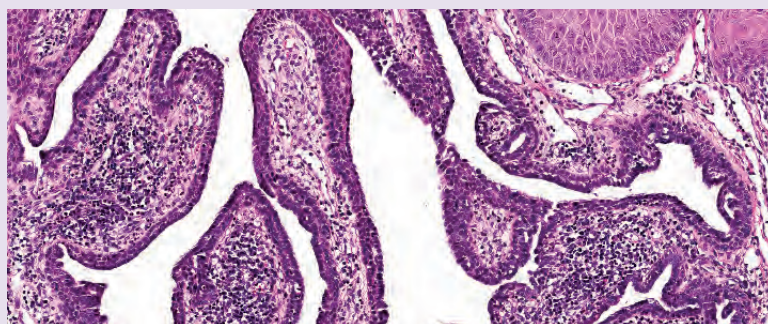
Acanthosis,
papillomatosis
and
hyperkeratosis



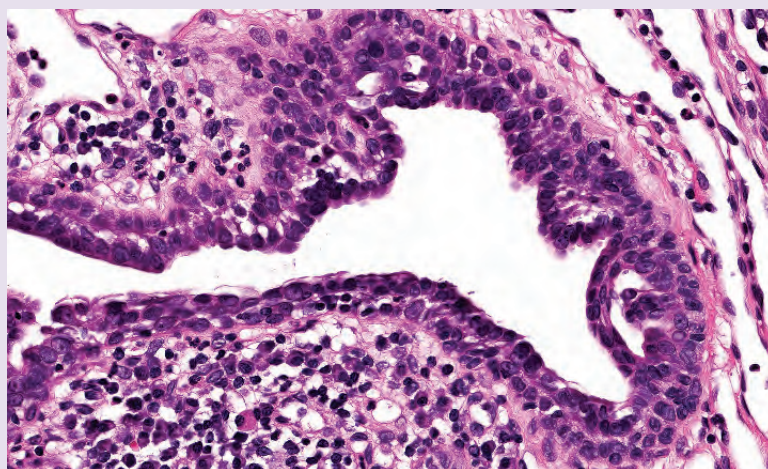
NEVI, HYPERPLASIAS, AND BENIGN ADNEXAL NEOPLASMS

Syringocystadenoma Papilliferum

Tubular apocrine invagination with protruding papillae (top and middle)



Decapitation secretion



Double-layered cyst wall with adjacent plasma cells

Cl: Verrucous papules on the face or head, often developing in sebaceous nevus of the scalp but also as sporadic lesions in a linear or plaque-like configuration. Crust formation due to secretion through draining fistulae.

Hi:

- Verrucous hyperkeratotic surface
- Finger-like double-layered tubules and ducts evolving from the surface epidermis and protruding into the deep dermis
- Small papillary projections protruding into the ductal lumina
- Connection with surface epithelium sometimes through dilated ostiofollicular spaces (seen in serial sections)
- Ducts and cystic spaces lined by double layer of apocrine epithelia with outer layer of myoepithelia
- Stromal reaction with inflammatory infiltrate containing many plasma cells

DD: Hidradenoma papilliferum; syringocystadenocarcinoma papilliferum, which shows an identical pattern to the benign variant but with additional marked pleomorphism and high mitotic activity of epithelial tumor cells.

References

- Ansai, S.I., Anan, T., Fukumoto, T., and Saeki, H. (2017) Tubulopapillary cystic adenoma with apocrine differentiation: a unifying concept for syringocystadenoma papilliferum, apocrine gland cyst, and tubular papillary adenoma. *Am J Dermatopathol* **39**(11): 829–37.
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MALIGNANT NEOPLASMS

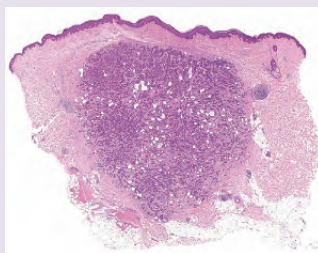
- Hsu, P.J., Liu, C.H., and Huang, C.J. (2003) Mixed tubulopapillary hidradenoma and syringocystadenoma papilliferum occurring as a verrucous tumor. *J Cutan Pathol* **30**(3): 206–10.
- Kasashima, S., Kawashima, A., and Fujii, T. (2016) Syringocystadenoma papilliferum of the male nipple. *J Cutan Pathol* **43**(8): 679–83.
- Kazakov, D. V., Bisceglia, M., Calonje, E., et al. (2007) Tubular adenoma and syringocystadenoma papilliferum: a reappraisal of their relationship. An interobserver study of a series, by a panel of dermatopathologists. *Am J Dermatopathol* **29**(3): 256–63.
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- Patterson, J.W., Straka, B.F., and Wick, M.R. (2001) Linear syringocystadenoma papilliferum of the thigh. *J Am Acad Dermatol* **45**(1): 139–41.
- Singh, U.R. (2000) Syringocystadenoma papilliferum mimicking breast carcinoma. *Am J Dermatopathol* **22**(1): 91.
- Xu, X.L., Zhang, G.Y., Zeng, X.S., Wang, Q., and Sun, J.F. (2010) A case of zonal syringocystadenoma papilliferum of the axilla mimicking verruca vulgaris. *Am J Dermatopathol* **32**(1): 49–51.

Malignant Adnexal Neoplasms Eccrine Differentiation

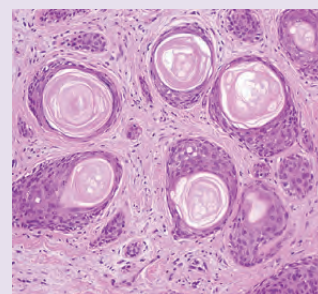
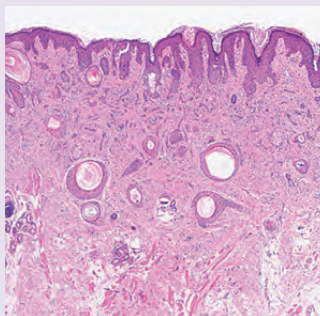
Microcystic Adnexal Carcinoma (Syringomatous Carcinoma, Sclerosing Sweat Ductal Carcinoma)

Scarring lesion
on the lower
lip (left)

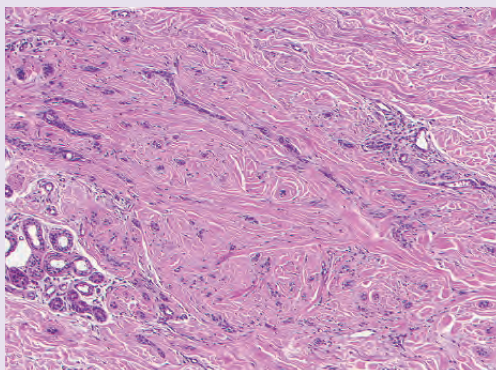
Deep reaching
dermal infiltrate
(right)



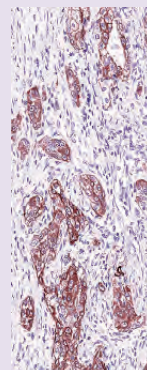
Epithelial strands,
cysts and
follicular
structures amidst
desmoplastic
stroma



Tumor strands
embedded in
sclerosing
stroma (left)



AE1/AE3
positive tumor
cells (right)



MALIGNANT NEOPLASMS

Cl: Small nodule or plaque, presenting usually on the face (chin, lip, cheek). Locally slowly growing but aggressive with deep invasion.

Hi: Predominant hallmarks: sclerotic collagenous stroma, microcysts, and pale elongated tumor strands. Biphasic differentiation (eccrine and follicular), allowing them in many cases to be distinguished from desmoplastic trichoepithelioma and from syringoma.

- Invasive, poorly circumscribed tumor with nests and strands of epithelial cells in the dermis
- Often with characteristic subepidermal tumor-free grenz zone
- Prominent subepidermal follicular microcysts
- Deeper parts with elongated slender strands of pale basaloid tumor cells
- Little cytological atypia, no mitoses, little proliferative activity (Ki67)
- Perineural involvement is common
- Immunophenotype: BerEP4 may be focally positive
- Pale cell variants may occur

DD: Morpheaform basal cell carcinoma; desmoplastic trichoepithelioma.

References

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Porocarcinoma (Malignant Poroma)

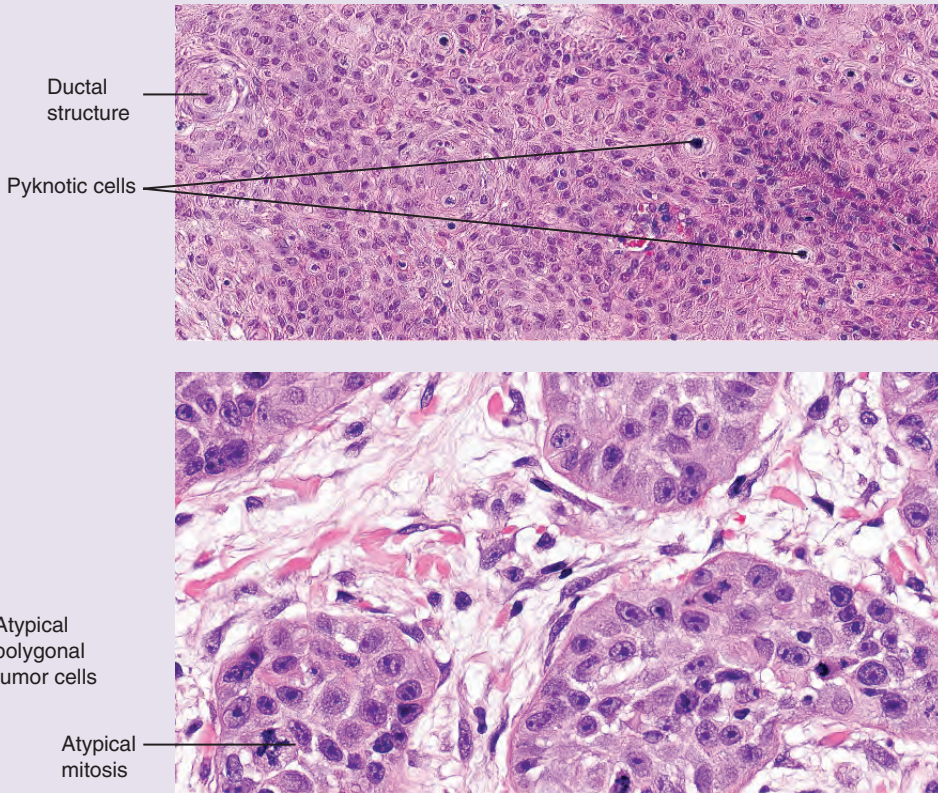
Poroid tumor pattern: proliferation of poroid tumor cells

Necrosis and ulceration



MALIGNANT NEOPLASMS

Porocarcinoma (Malignant Poroma)



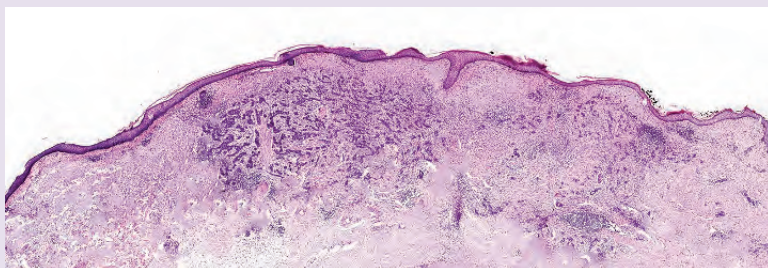
Cl: Ulcerated tumor, preferentially localized on the legs of elderly individuals. Tendency to local epidermotropic and lymph node metastases. Poor prognosis. May evolve from a pre-existing poroma.

Hi:

- Invasive poroid tumor with marked pleomorphism and sharp lateral demarcation towards regular epidermis
- Often multicentric with closely grouped tumor strands evolving from epidermis
- Poroid proliferation of pleomorphic tumor cells
- Marked cellular atypia with hyperchromatic nuclei similar to Bowen carcinoma
- Multiple mitoses
- Ductal differentiation and features of eccrine poroma may be lacking

Eccrine (Mucinous) Carcinoma

Infiltrative growing tumor



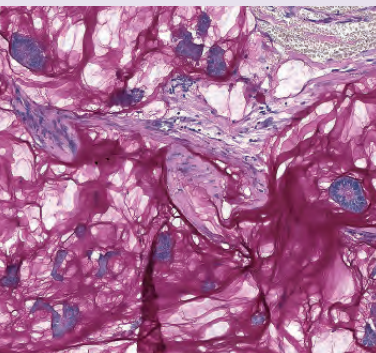
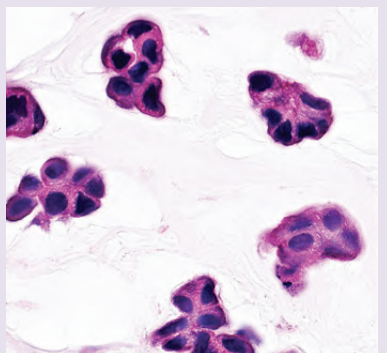
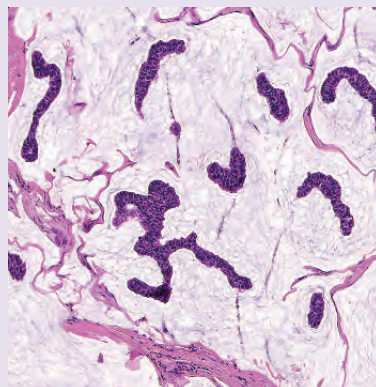
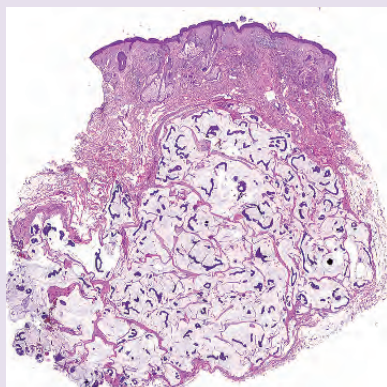
MALIGNANT NEOPLASMS

Eccrine (Mucinous) Carcinoma

Islands of atypical cells with ductal features in mucinous stroma (left and right)

Tumor cells lying in “puddles of mucin” (mid right, bottom left)

PAS-positive mucinous stroma (right)



Cl: Skin-colored or red nodule, preferentially in the head and neck region. Some of the cases may represent cutaneous metastases of internal carcinoma (breast, gastrointestinal).

Hi:

- Both infiltrative and nodular tumor with ill-defined margins
- Irregular nests and anastomosing slender strands of atypical basaloid tumor cells with hyperchromatic nuclei
- Large amounts of mucin representing most of the tumor stroma
- Basaloid epithelial tumor strands and nests lying in “puddles of mucin”
- Moderate mitotic activity

DD: Metastasis from mucinous carcinoma of the breast or gastrointestinal tract; mucin-rich cystic basal cell carcinoma; endocrine mucin-producing tumor.

References

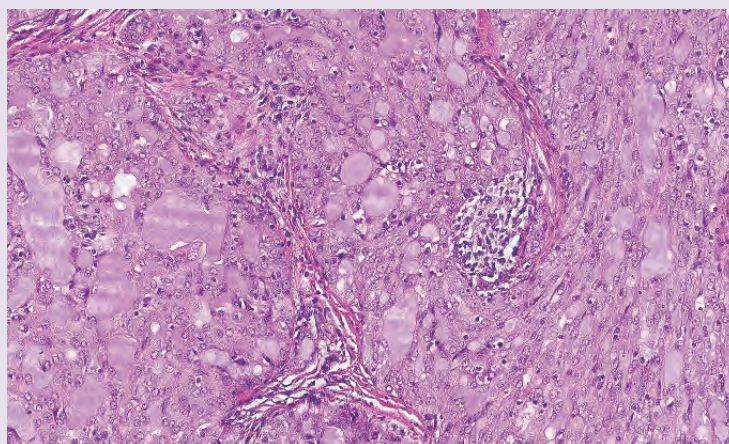
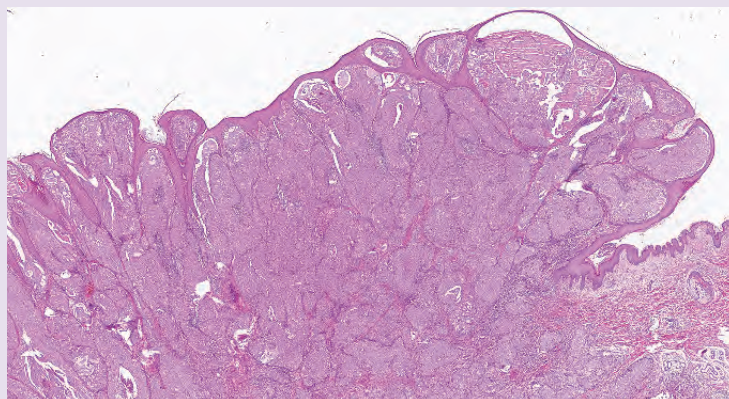
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MALIGNANT NEOPLASMS

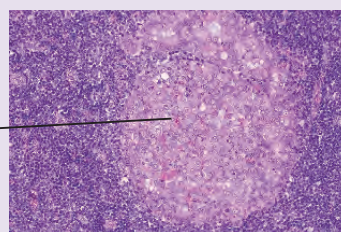
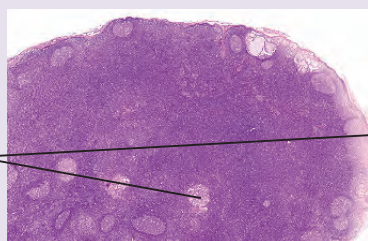
Apocrine Differentiation

Apocrine (Hidr-)Adenocarcinoma (Mucinous)

Lobules of highly secretory atypical cells



Lymph node metastasis



CI: Nodule, sometimes ulcerated, preferentially in the head and neck area or the extremities. Frequent metastases in the regional lymph nodes.

Hi: Malignant counterpart of solid hidradenoma.

- Multilobulated acrospiroma-like tumor with clonal pleomorphism and high mitotic activity,

which may be restricted to clonal parts of the tumor

- Focal hyperchromasia in conjunction with pleomorphism and many mitoses are leading features
- Infiltrative growth pattern in advanced lesions
- Focal necroses in advanced lesions

HYPERPLASIAS AND HAMARTOMAS

References

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Sebaceous Differentiation

Epithelial tumors with sebaceous differentiation usually present with lobules of mature sebocytes, in particular in the sebaceomas which comprise the entities formerly known as sebaceous epithelioma and sebaceous adenoma. However, there is a vast array of other epithelial tumors, such as

basal cell carcinoma, that may show discrete signs of sebaceous differentiation that may easily be overlooked. As a rule of thumb, a single epithelial cell with intracytoplasmic adipophilin-positive vacuoles may be taken as an indicator of sebaceous differentiation in a benign or malignant epithelial tumor. Usually, there are small clusters of adipophilin-positive tumor cells which allow straightforward differentiation from necrotic carcinoma cells that may also show sebaceous and fatty deposits within the cytoplasm. Immunohistochemical staining for adipophilin in the context of an epithelial tumor has evolved as the method of choice for defining sebaceous differentiation.

References

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- Ostler, D.A., Prieto, V.G., Reed, J.A., Deavers, M.T., Lazar, A.J., and Ivan, D. (2010). Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. *Mod Pathol* **23**(4): 567–73.
- Tetzlaff, M.T. (2018) Immunohistochemical markers informing the diagnosis of sebaceous carcinoma and its distinction from its mimics: adipophilin and Factor XIIIa to the rescue? *J Cutan Pathol* **45**(1): 29–32.

HYPERPLASIAS AND HAMARTOMAS

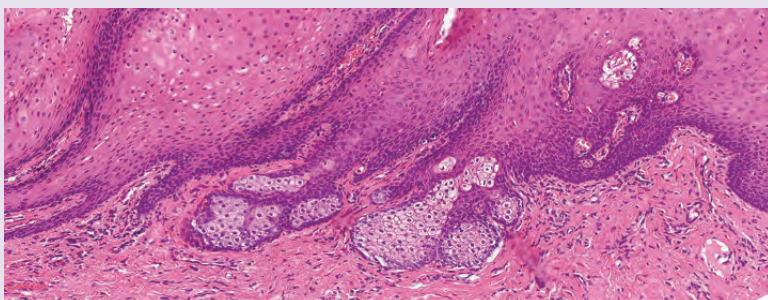
Hyperplasias and Hamartomas

Ectopic (Heterotopic) Sebaceous Glands (Fordyce Glands)

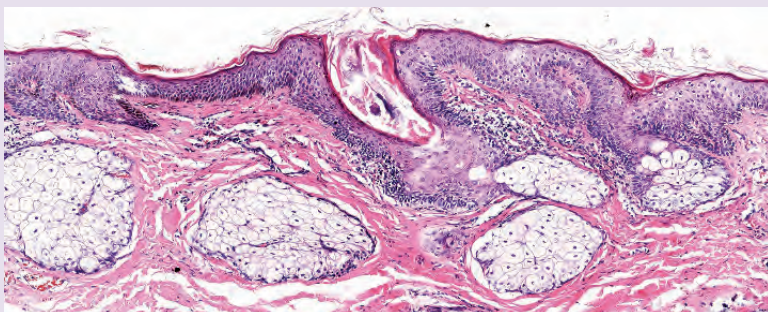
Fordyce glands
on the lip (left)
and on the penile
sulcus coronarius
(right)



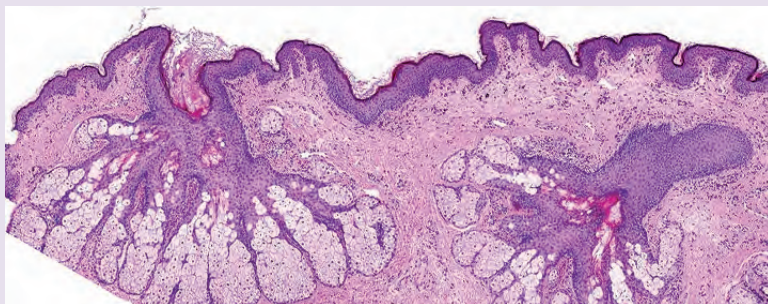
Fordyce
glands (lip)



Montgomery
glands of the
areola mammae



Hyperplastic
penile ectopic
sebaceous
glands



HYPERPLASIAS AND HAMARTOMAS

Various localisations: lip (Fordyce's spot); Montgomery glands of the areola mammae; ectopic glands on the penile sulcus coronarius.

Cl: Small, 2–3 mm yellow papules on the buccal mucosa of the lips and on the external mucosa of the genitalia. They are present in most individuals and do not have any nosological impact.

Hi: Transitional or mucosal epithelium showing normal sebaceous glands or hyperplasia of sebaceous glands. There are no associated hair follicles ("isolated sebaceous glands").

References

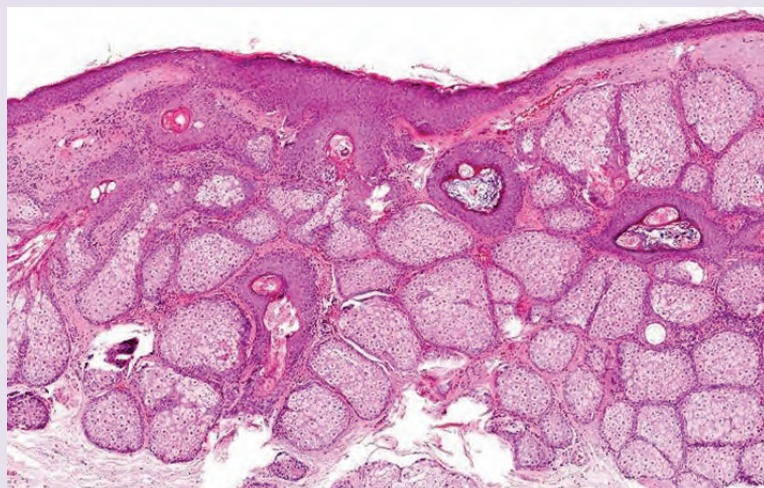
- Moosbrugger, E.A. and Adams, B.B. (2011) Disseminated eruption of ectopic sebaceous glands following Stevens-Johnson syndrome. *J Am Acad Dermatol* **65**(2): 446–8.
- Tschen, J.A., Schulze, K.E., and Chiao, N. (2006) Ectopic sebaceous gland: a developmental anomaly. *J Cutan Pathol* **33**(7): 519–21.

(Senile) Sebaceous Gland Hyperplasia

Yellow papules
with central dell
(inset)



Hyperplastic
sebaceous
glands
connected with
the epidermis
through a single
follicular duct



HYPERPLASIAS AND HAMARTOMAS

Cl: Multiple disseminated yellow or skin-colored papules with central dent, preferentially on the forehead or cheeks of elderly men. No malignant potential.

Hi:

- Aggregates of hyperplastic sebaceous glands
- Single follicular sebaceous duct leading to the surface
- Mature sebaceous epithelia
- Holocrine secretion

DD: Verrucae planae; molluscum contagiosum.

References

- De Villez, R.L. and Roberts, L.C. (1982) Premature sebaceous gland hyperplasia. *J Am Acad Dermatol* **6**(5): 933–5.
- Kudoh, K., Hosokawa, M., Miyazawa, T., and Tagami, H. (1988) Giant solitary sebaceous gland hyperplasia clinically simulating epidermoid cyst. *J Cutan Pathol* **15**(6): 396–8.
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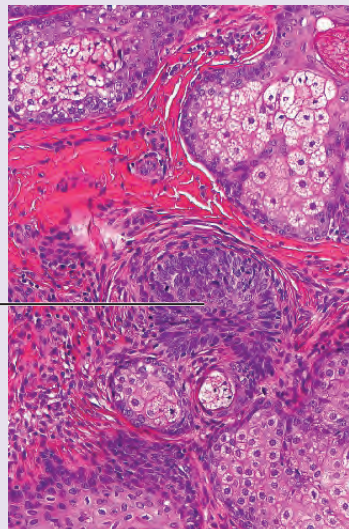
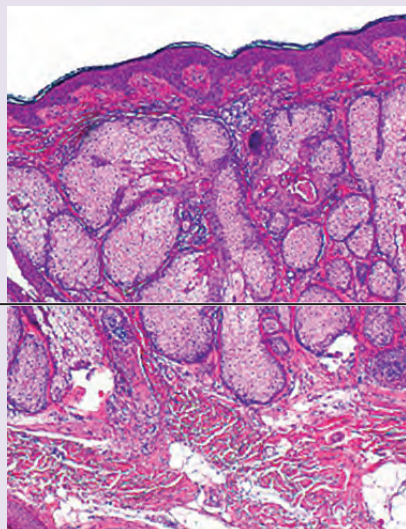
Nevus Sebaceous (Jadassohn)

Yellow plaque with papillomatous surface



Multiple hyperplastic sebaceous glands. Lack of hair follicles (left)

Rudimentary papilla; trichoeipithelial structure



BENIGN NEOPLASMS

Cl: Hairless yellowish plaque with papillomatous surface, preferentially on the scalp, present since birth. Ductal, sebaceous, and hair follicle tumors may arise in sebaceous nevi.

Hi: Clusters of sebaceous glands but no mature hair follicles. Basaloid and follicular induction may occur. The surface can be papillomatous and acanthotic and resemble a seborrheic keratosis. There may be strong similarity with superficial basal cell carcinoma and morphological overlap with trichoblastoma. Genuine trichoblastoma – usually larger and hyperpigmented – and trichoblastoma-like hamartomatous tumors may be inherent parts of nevus sebaceous. Trichilemmoma and tubular apocrine adenomas of smaller size are other autochthonous tissue components of large nevus sebaceous.

DD: Verrucous epidermal nevus.

References

- Cribier, B., Scrivener, Y., and Grosshans, E. (2000) Tumors arising in nevus sebaceus: a study of 596 cases. *J Am Acad Dermatol* **42**(2 Pt 1): 263–8.
- Dore, E., Noe, M.H., and Swick, B.L. (2015) Trichoblastoma, syringocystadenoma papilliferum, desmoplastic trichilemmoma and tumor of the follicular infundibulum with signet-ring cells, all arising in nevus sebaceus. *J Cutan Pathol* **42**(9): 645–51.
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- Kaddu, S., Schaeppi, H., Kerl, H., and Soyer, H.P. (2000) Basaloid neoplasms in nevus sebaceus. *J Cutan Pathol* **27**(7): 327–37.
- Sellheyer, K., Cribier, B., Nelson, P., Kutzner, H., and Rutten, A. (2013) Basaloid tumors in nevus sebaceus revisited: the follicular stem cell marker PHLDA1 (TDAG51) indicates that most are basal cell carcinomas and not trichoblastomas. *J Cutan Pathol* **40**(5): 455–62.

Variant: Pilo-Sebaceous Hamartoma

Cl: Variant of nevus sebaceous showing a conglomerate of sebaceous and pilar components. Hair follicles are present.

Hi:

- Intradermally located tumor
- Centrally located mesenchymal part: fat, blood vessels, fibrous tissue
- Malformed follicles with prominent sebaceous glands in the periphery

Reference

- Raghu, P., Tran, T.A., Rady, P., Tying, S., and Carlson, J.A. (2012) Ileostomy-associated chronic papillomatous dermatitis showing nevus sebaceous-like hyperplasia, HPV 16 infection, and lymphedema: a case report and literature review of ostomy-associated reactive epidermal hyperplasias. *Am J Dermatopathol* **34**(7): e97–102.

Benign Neoplasms Sebaceous Adenoma

This term should not be confused with adenoma sebaceum, which is angiofibroma in tuberous sclerosis. Recently, benign sebaceous tumors have been subsumed under the umbrella term *sebaceoma* that comprises sebaceous adenoma (pale sebaceous tumor with predominance of mature sebocytes) and sebaceous epithelioma (dark sebaceous tumor with predominance of basophilic germinative sebocytes).

Cl: Yellowish, occasionally eroded and crusted papule or nodule preferentially on the periorbital area of the face or on the scalp of adult patients, but also in other localisations. Association with Muir–Torre syndrome possible.

Hi:

- Nodule composed of enlarged sebaceous glands
- Sebaceous-ductal connection with the epidermis
- Arrangement around a central follicle
- Sebaceous maturation with foamy holocrine sebocytes in the center
- Basaloid germinative sebocytes in the periphery

DD: Basal cell carcinoma; sebaceous hyperplasia; mixed sebaceous tumor (tubular adenoma of the skin with follicular and sebaceous differentiation) has been reported.

References

- Azevedo, R.S., Almeida, O.P., Netto, J.N., et al. (2009) Comparative clinicopathological study of intraoral sebaceous hyperplasia and sebaceous adenoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **107**(1): 100–4.
- Kazakov, D.V., Mukensnabl, P., and Michal, M. (2006) Tubular adenoma of the skin with follicular and sebaceous differentiation: a report of two cases. *Am J Dermatopathol* **28**(2): 142–6.
- Marques-da-Costa, J., Campos-do-Carmo, G., Ormiga, P., Ishida, C., Cuzzi, T., and Ramos-e-Silva, M. (2015)

BENIGN NEOPLASMS

Sebaceous adenoma: clinics, dermatoscopy, and histopathology. *Int J Dermatol* **54**(6): e200–202.

Somashekara, K.G., Lakshmi, S., and Priya, N.S. (2011) A rare case of sebaceous adenoma of the palate, with literature review. *J Laryngol Otol* **125**(7): 750–2.

Takayama, K., Usui, Y., Ito, M., Goto, H., and Takeuchi, M. (2013) A case of sebaceous adenoma of the eyelid

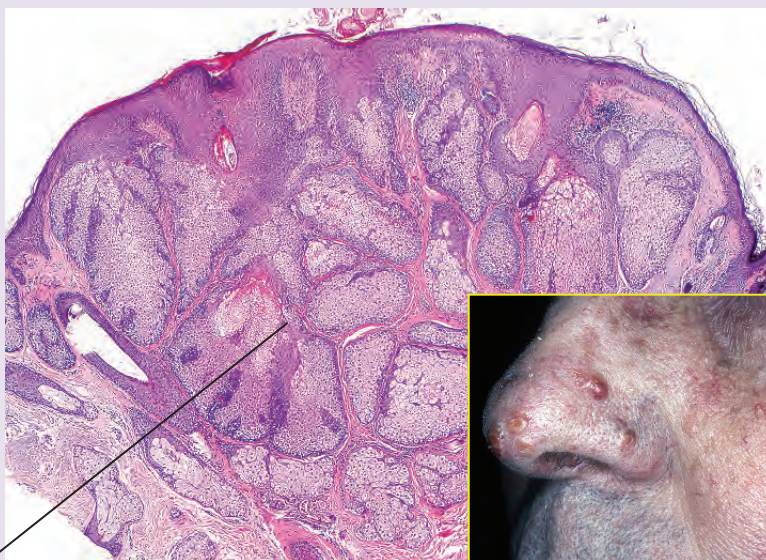
showing excessively rapid growth. *Clin Ophthalmol* **7**: 667–70.

Terrell, S., Wetter, R., Fraga, G., Kestenbaum, T., and Aires, D.J. (2007) Penile sebaceous adenoma. *J Am Acad Dermatol* **57**(2 Suppl): S42–3.

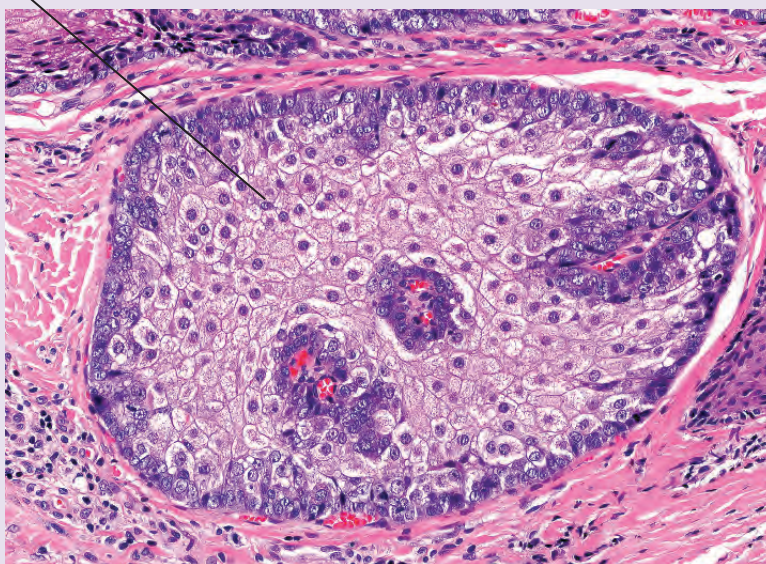
Muir–Torre Syndrome

Multiple adenomas in the face (inset)

Nodule composed of enlarged sebaceous glands



Inset: Muir-Torre syndrome



BENIGN NEOPLASMS

Cl: Germline mutation, leading to association of multiple sebaceous tumors (sebaceous hyperplasias, sebaceous adenomas, and carcinomas) and/or extrafacial (mostly trunk) keratoacanthomas with visceral carcinomas (mostly colon).

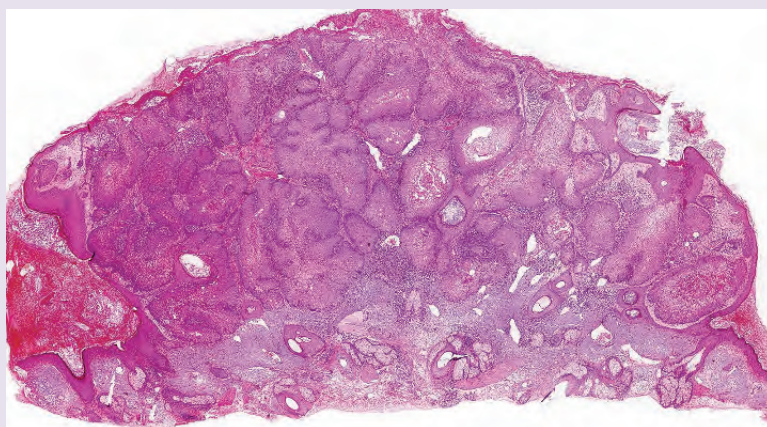
Hi: In most cases, histopathological changes correspond to banal sebaceous hyperplasias, sebaceous adenomas or straightforward sebaceous carcinomas. A specific Muir–Torre-associated “landmark tumor” is cystic sebaceous tumor (former classification: cystic sebaceous adenoma or adenocarcinoma). Cystic sebaceous tumor is large, nodular, proliferates like an epidermal cyst, and shows large

masses of mature adipocytes within its cyst wall and in the cyst cavity, which may be totally obstructed. There is a sharp and smooth outer border with germinative sebocytes.

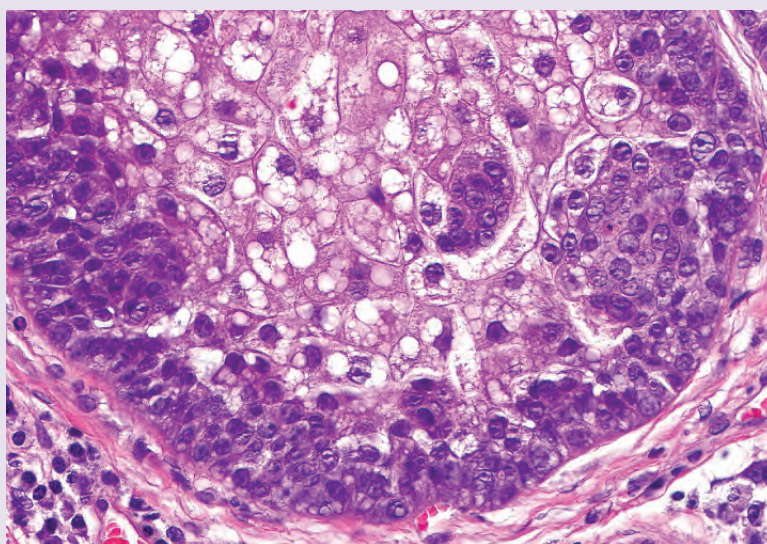
Comment: Immunohistochemical testing for expression of DNA mismatch repair proteins in sebaceous tumors of Muir–Torre patients and suspected patients is paramount: in Muir–Torre-associated sebaceous lesions, at least one set of the DNA mismatch repair proteins MSH2/MSH6 and MLH1/PMS2 is not expressed. These findings should be corroborated by additional molecular test for microsatellite instability.

Sebaceous Epithelioma (Sebaceoma)

Nodule composed of enlarged sebaceous glands



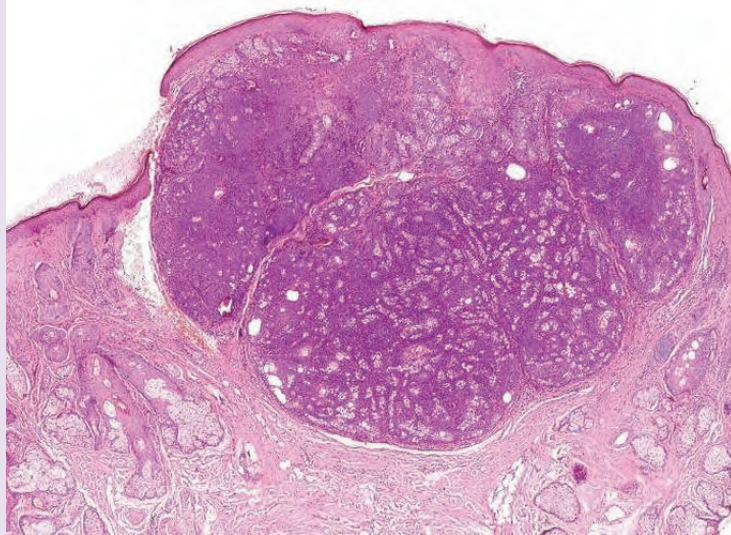
Foamy sebaceous cells in the center, surrounded by basaloid germinative cells in the periphery



BENIGN NEOPLASMS

Sebaceous Epithelioma (Sebaceoma)

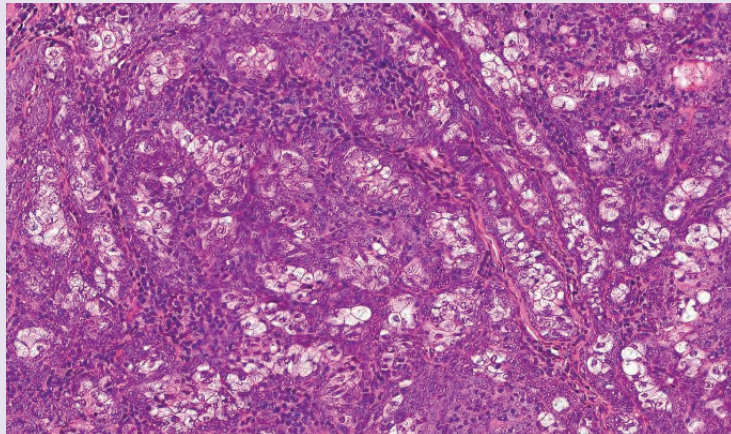
Nodule with
lobular structure



Lace-like pattern

Dark basaloid
immature
sebaceous cells

Clear mature
sebaceous cells



Cl: Slowly growing papule or nodule with preferential localisation in the head and neck area, clinically simulating basal cell epithelioma or other epithelial tumors.

Hi:

- Basal cell carcinoma-like basaloid epithelial tumor with focal sebaceous differentiation (germinative sebocytes)
- Rippled pattern of basaloid germinative sebocytes showing EMA-positivity and little or no intracytoplasmic adipophilin-positive fatty deposits.
- Focal, mostly peripheral, sebaceous differentiation (germinative sebocytes)

- BerEP4 negative in contrast to basal cell carcinoma
- Adipophilin expression within germinative sebocytes

Immunohistochemistry: Adipophilin serves as a useful marker of sebaceous differentiation in various epithelial tumors.

References

- Chuang, H.C., Kao, P.H., Huang, Y.L., Lee, L.Y., and Kuo, T.T. (2014) Desmoplastic sebaceoma arising from nevus sebaceus: a new variant. *J Cutan Pathol* **41**(6): 509–12.

MALIGNANT NEOPLASMS

Fan, Y.S., Carr, R.A., Sanders, D.S., Smith, A.P., Lazar, A.J., and Calonje, E. (2007) Characteristic Ber-EP4 and EMA expression in sebaceoma is immunohistochemically distinct from basal cell carcinoma. *Histopathology* **51**(1): 80–6.

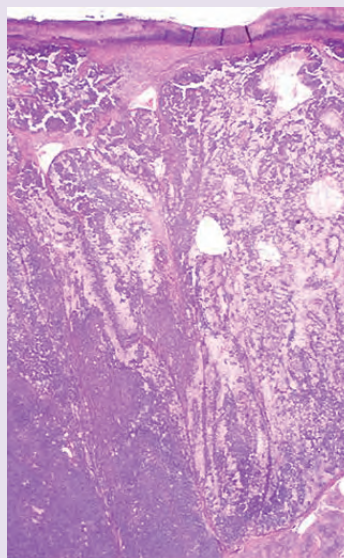
Misago, N. and Narisawa, Y. (2001) Rippled-pattern sebaceoma. *Am J Dermatopathol* **23**(5): 437–43.

Malignant Neoplasms

Sebaceous Carcinoma

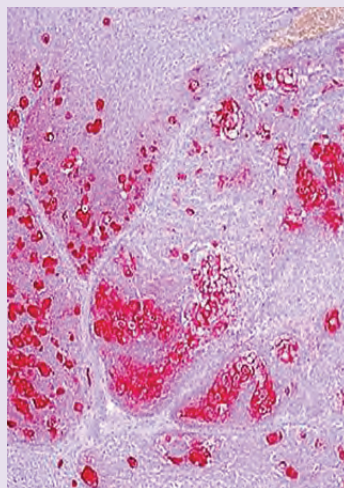
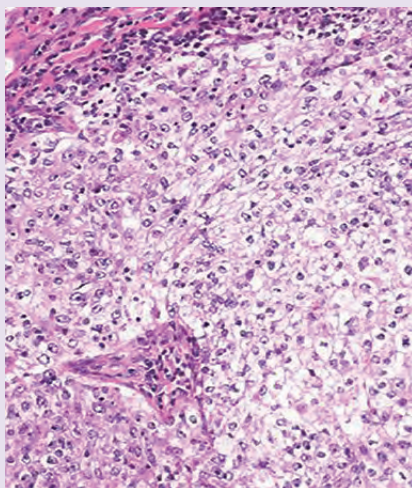
Indurated
plaque-like
tumor on the
trunk (left)

Mixed labyrinthine
and solid tumor
pattern (right)



Sebaceous
differentiation
with “Clear”
tumor cells
(left)

Atypical
EMA-positive
sebaceous
cells (right)



NEVI, HYPERPLASIA, AND HAMARTOMAS

Cl: Aggressive tumor occurring on the eyelid and in extraocular localisations. Risk for metastases is high; mortality rate 10–20%. Predilection for Asian individuals. Ocular sebaceous carcinoma usually is considered to be more aggressive than extraocular sebaceous carcinoma.

Hi:

- Tumors showing basaloid, sebaceous, and/or squamous differentiation
- Morphological blending with classic squamous cell carcinoma pattern may occur
- Presence of atypical foamy or vacuolated atypical sebocytes in all variants of sebaceous carcinoma
- Intraepidermal pagetoid spread of clear cell-like atypical sebocytes is restricted to the ocular variant of sebaceous carcinoma; it can be mistaken for pagetoid solar keratosis or carcinoma *in situ*
- Extraocular sebaceous carcinoma shows solid, highly pleomorphic tumor pattern with high proliferative activity

Immunohistochemistry: Common denominator of all sebaceous carcinoma variants is expression of adipophilin by neoplastic sebocytes.

DD: Cutaneous PEComa*; metastatic clear cell carcinomas of visceral origin (renal cell carcinoma); clear cell variants of other tumors (melanoma, carcinoma); genuine squamous cell carcinoma with necrotic keratinocytes that may imitate immature sebocytes (adipophilin-positive necrosis).

* PEComa family comprises a group of related mesenchymal neoplasms, including angiomyolipoma, lymphangiomyomatosis, and clear cell tumor of the lung.

References

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Hair Follicle Differentiation

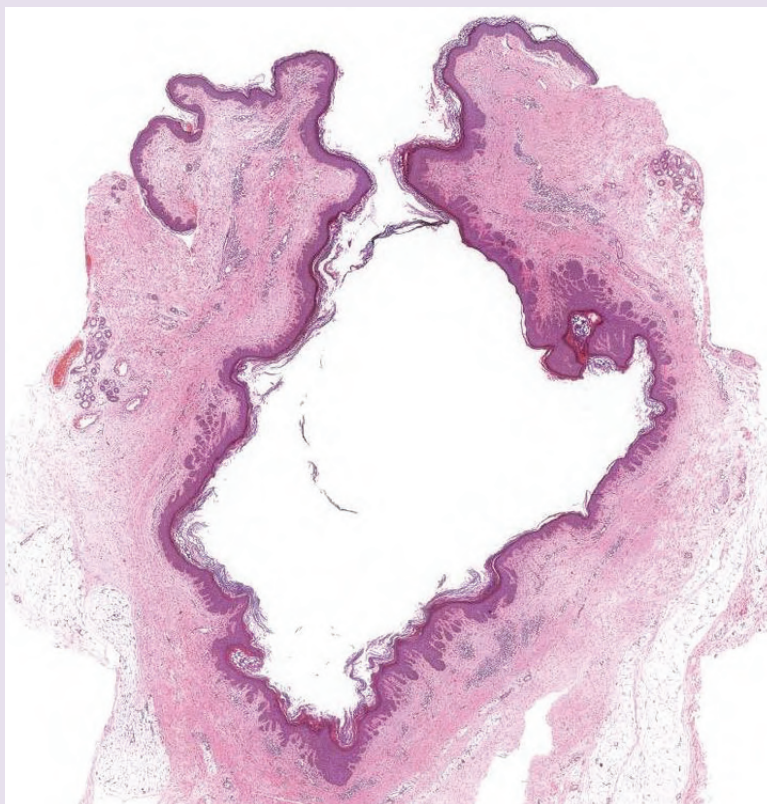
Nevi, Hyperplasia, and Hamartomas Hair Follicle Nevus

Cl: Localisation: head, neck; area of hypertrichosis.

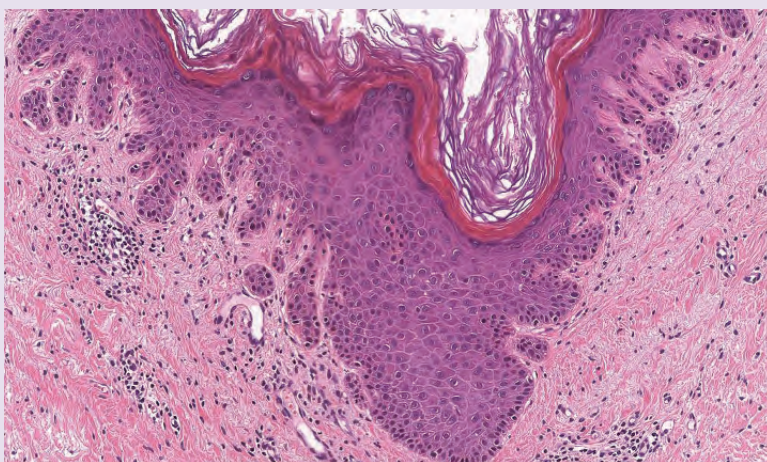
Hi: Group of normal vellus hairs.

Conical Infundibular Acanthoma (Giant Dilated Pore of Winer)

Cavity, widely open to the skin surface



Slight irregular acanthosis and papillomatosis



BENIGN NEOPLASMS

Cl: Conical triangular, comedo-like dilation of a follicle on the face, neck or upper part of the chest of older individuals.

Hi:

- Dilated ostiofollicular cyst
- Wide open to the skin surface
- Dilated ostium may be filled with cornified material
- Cavity wall is normal or shows irregularly acanthotic infundibular rete ridges
- Slightly papillomatous
- Small sebaceous glands or vellus hair may be included in the wall

- Melanin pigmentation

DD: Pilar sheath acanthoma; superficial follicular epithelial cyst.

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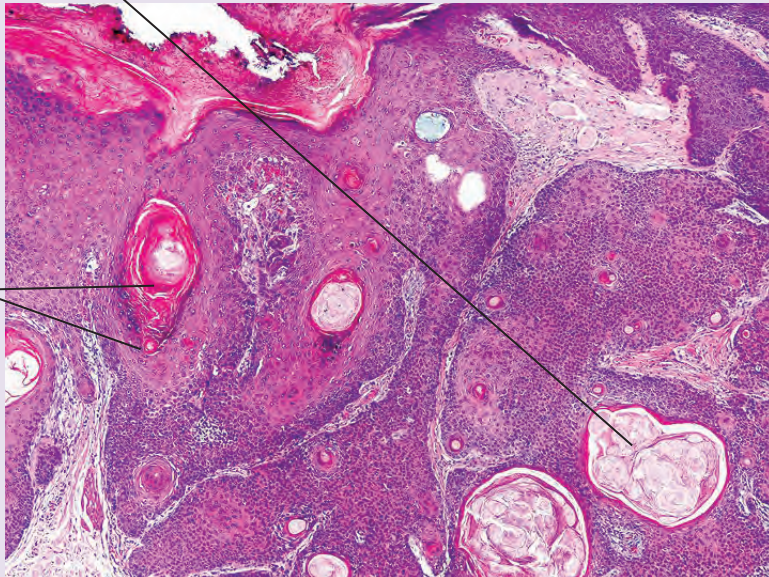
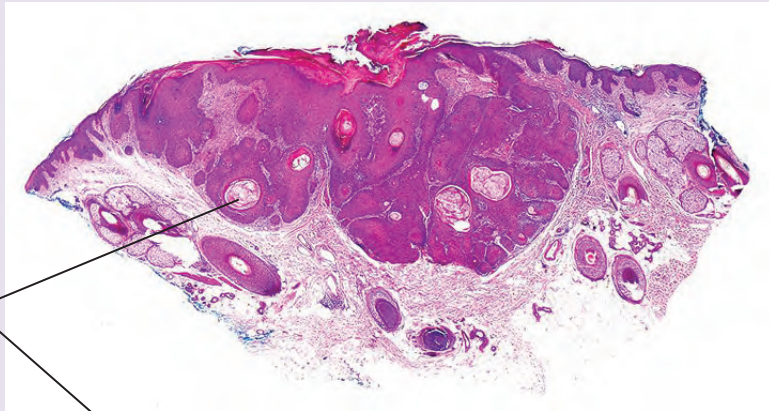
Benign Neoplasms

Pilar Sheath Acanthoma

Pseudocystic invagination, acanthotic proliferation

Horn cysts

Terminal hair and pale infundibular cells



BENIGN NEOPLASMS

Cl: Solitary broad-based papule or nodule, preferentially on the upper lip of older individuals. There may be a central porus-like cyst filled with keratotic material.

Hi:

- Cystic invagination of the epidermis, filled with keratotic material
- Acanthotic epithelial cyst wall with markedly enlarged rete ridges
- Epithelia showing root sheath differentiation
- No mature hair follicle present

Immunohistochemistry: Homogeneous positivity for CK17.

DD: Trichofolliculoma; conical infundibular acanthoma; dilated pore of Winer; giant comedo.

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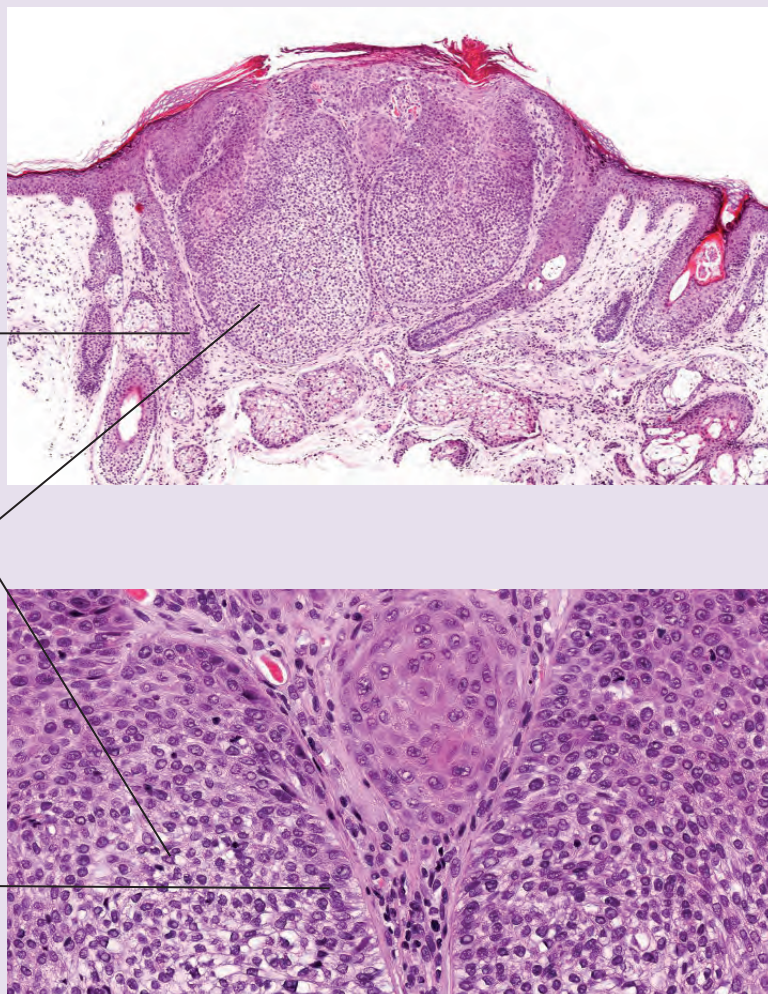
Trichilemmoma (Tricholemmoma)

Folliculocentric proliferation of basaloid cells

Pincer-like lip formation

Pale glycogen rich cells

Peripheral palisading



BENIGN NEOPLASMS

Cl: Solitary trichilemmoma presents mostly in adults as a small exophytic verrucous papule, several mm in size and located preferentially in the head and neck region. Multiple trichilemmomas are found in Cowden's disease (multifocal hamartomatous polyposis of the intestine; autosomal PTEN mutation).

Hi:

- Circumscribed folliculocentric proliferation of pale basaloid isomorphic cells with no proliferative activity
- Bilateral epidermal collarette
- Thickened basement membrane beneath the proliferation may be a good diagnostic criterion
- Tumor silhouette may simulate a superficial pale cell basal cell carcinoma
- Normal basal layer with peripheral palisading ("BCC-like")
- Negative for (BCC-marker) BerEP4
- Desmoplastic stroma in desmoplastic trichilemmoma

DD: Verruca vulgaris; inverted follicular keratosis; acrospiroma; basal cell carcinoma.

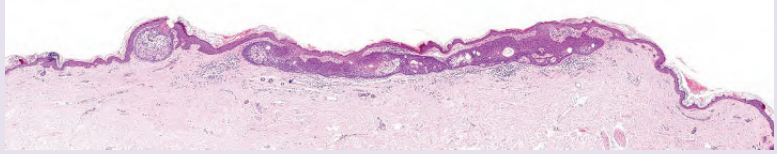
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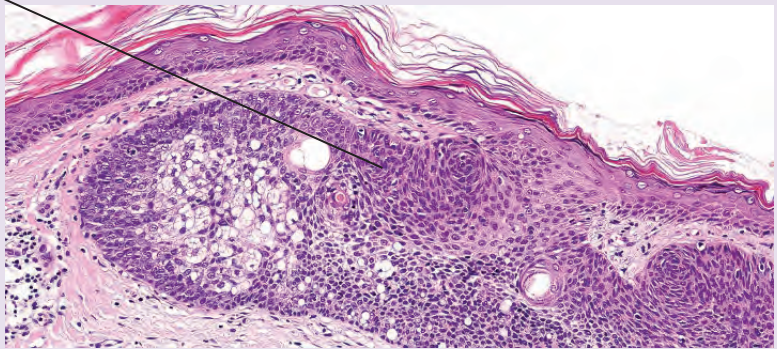
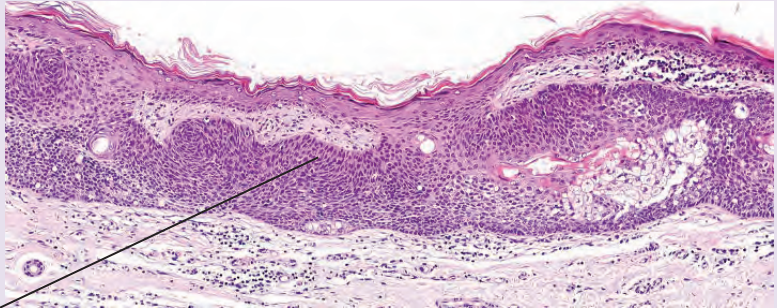
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Tumor of the Follicular Infundibulum (Infundibuloma)

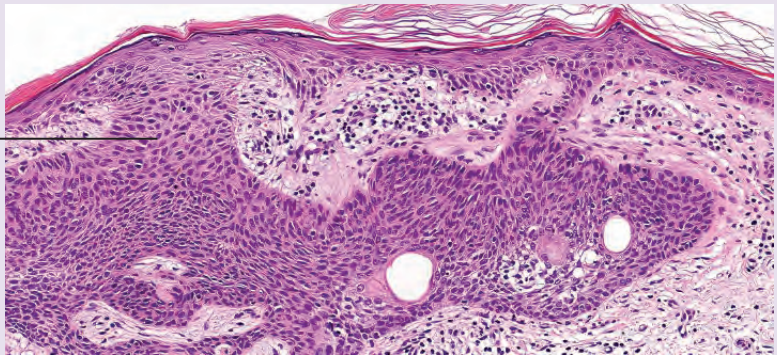
Shallow
acanthotic
subepidermal
plate



Bridging
interconnections
and connections
with the
epidermis



Pale isthmoid
epithelial cells



CI: Papule or plaque on the head or face of elderly individuals. Multiple eruptive lesions can occur in other localisations. It is considered by some to be a variant of basal cell carcinoma.

Hi:

- Interconnecting “streamer-like” pale basaloid epithelial strands in a horizontal array, restricted to the subepidermal cutis

BENIGN NEOPLASMS

- Multifocal connections to the overlying epidermis
- Predominant pale basaloid epithelia corresponding to outer root sheath epithelia
- Various types of appendageal differentiation may be present
- Positivity for calretinin

DD: Basal cell carcinoma; trichilemmoma; flat seborrheic keratosis.

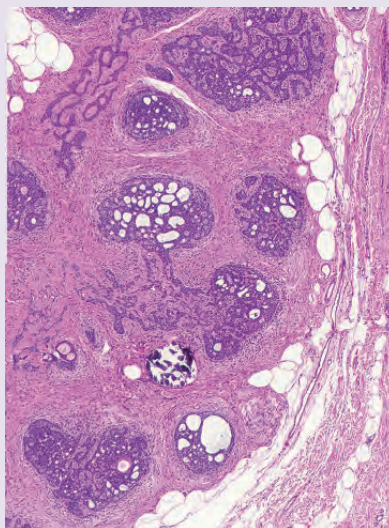
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Trichoepithelioma (Superficial Trichoblastoma)

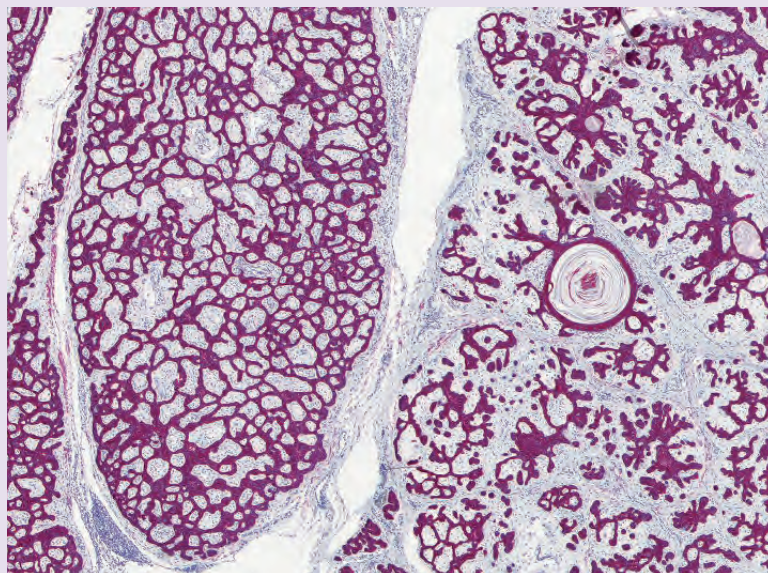
Tumor with telangiectases on the nose (left)

Strands and nests of basaloid cells (right)



Trichoepithelioma (Superficial Trichoblastoma)

Basaloid tumor nests in a lacelike pattern, BerEP4+



Cl: Skin-colored or yellowish-red, slowly growing papule, preferentially on the face of children or young adults. Presence of multiple lesions is typically seen in Spiegler Brooke syndrome (angiofibromas of epithelioma adenoides cysticum).

Hi:

- Lobules of strands and nests of basaloid cells in lace-like or cribriform pattern
- Peripheral palisading
- Keratinous microcysts
- Focal differentiation into hair bulbs
- Stromal reaction showing eosinophilic dense collagenous tissue
- Focal differentiation of papillary mesenchymal bodies, i.e. nestin-positive conglomerates of hair papilla-like fibroblasts with adjacent basaloid epithelia, simulating an abortive hair bulb

DD: Basal cell carcinoma; trichofolliculoma; basaloid follicular hamartoma.

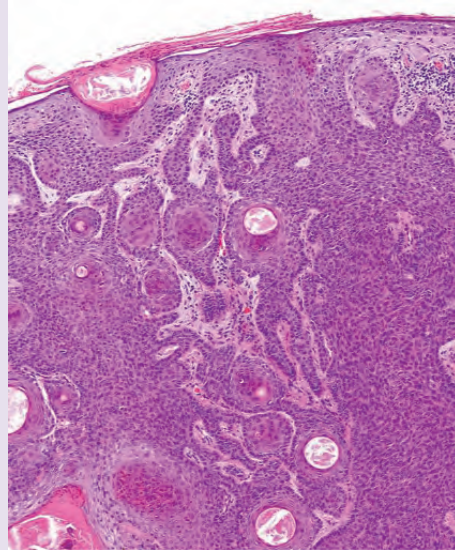
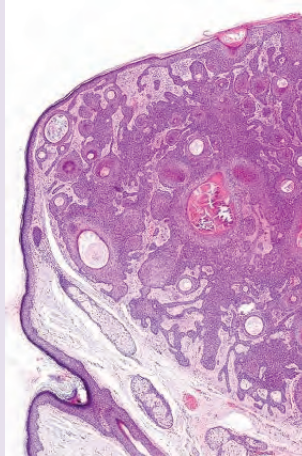
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BENIGN NEOPLASMS

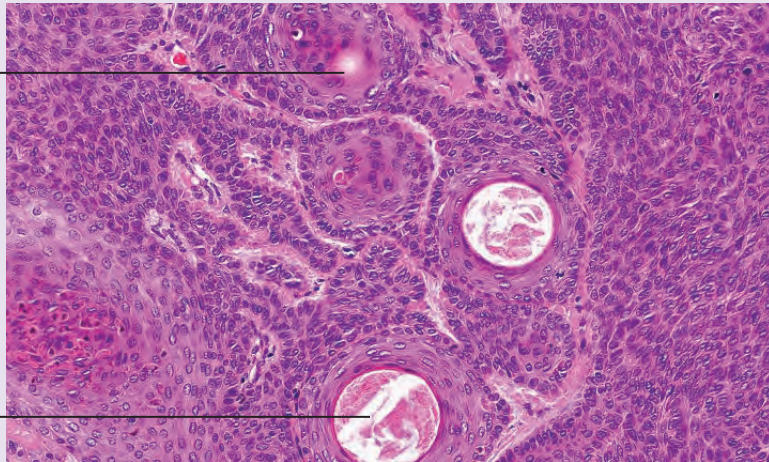
Trichoblastoma (Trichoblastic Fibroma; Immature Trichoepithelioma)

Vertical growth of well circumscribed proliferation of basaloid cells



Incomplete follicular differentiation

Follicular microcyst



Cl: Trichoblastoma frequently originates in a sebaceous nevus; it can occur at any site and may reach large size. Ulceration is exceedingly rare. Many trichoblastomas occur independent of the nevus on the scalp of middle-aged to elderly men.

Hi:

- Well-circumscribed vertically growing tumor, with basaloid tumor cells arranged in cords, sheets or clusters, branching and anastomosing
- Connected to the epidermis
- Characteristic zonation of individual tumor nests and lobules ("pizza sign") with an outer rim of deep basophilic epithelia and a pale center, often containing melanophages
- Nestin-positive papillary mesenchymal bodies
- CK20-positive Merkel cells distributed throughout the tumor in a starry sky-like pattern
- Amorphous eosinophilic debris and mucomyxoid stromal alterations may be present
- Different histological patterns exist:
 - Small nodular
 - Large nodular
 - Adamantinoid trichoblastoma, with lymphocytic infiltrate within tumor nests (outdated)

BENIGN NEOPLASMS

synonyms are lymphoepithelial tumor or cutaneous lymphadenoma)

- Cystic
- Papillary trichoblastoma
- Racemiform (like an elk's antlers)
- Cribriform (like a sieve)

- Retiform (like a net)

- Rippled pattern

- Clear cell trichoblastoma

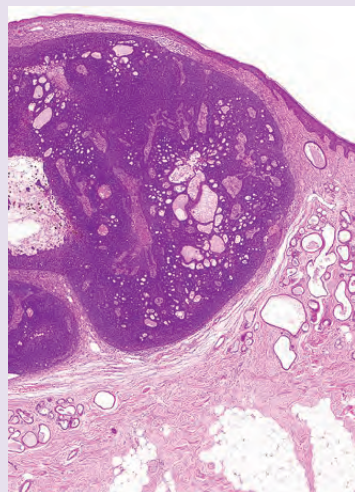
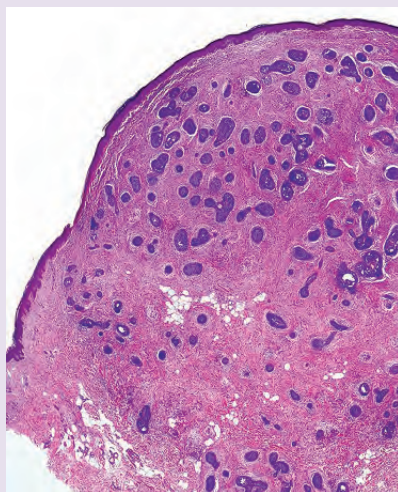
- Pigmented trichoblastoma

- Desmoplastic trichoblastoma (see below)

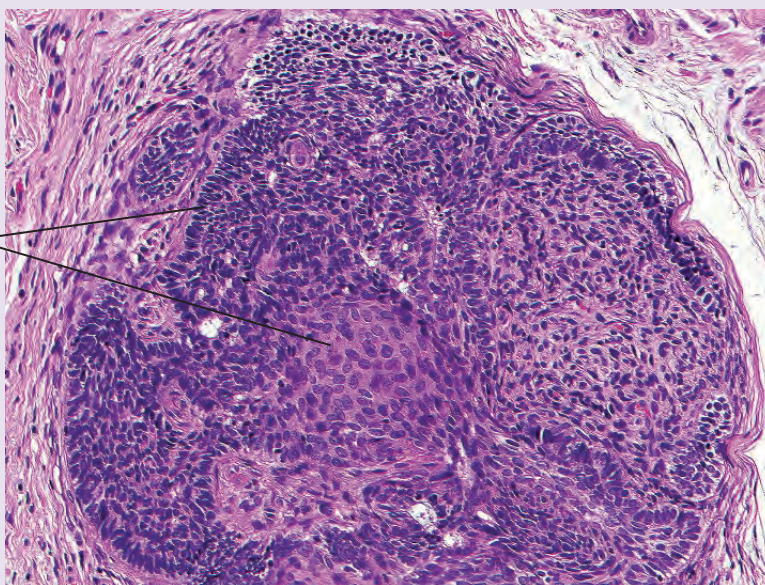
DD: Basal cell carcinoma.

Trichoblastoma, Small and Large Nodular

Well circumscribed tumor with small (left) or large (right) nodules of basaloid cells and compact stroma

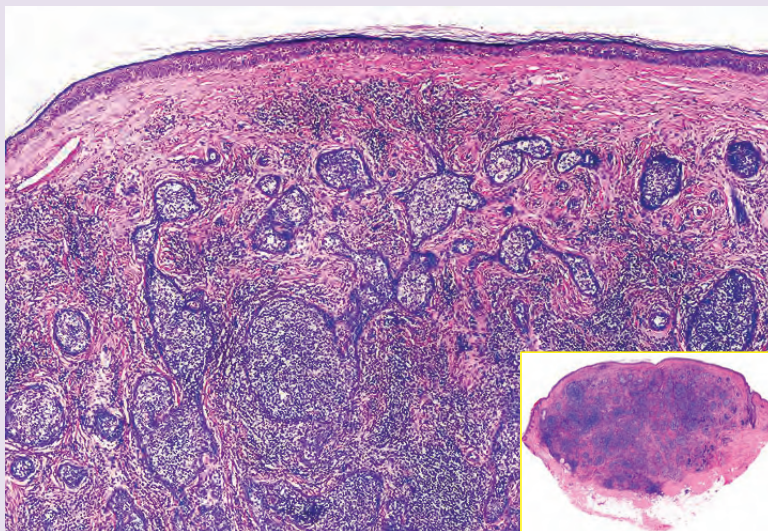


"Pizza sign": palisading dark cells around pale center; hair germs and primitive hair papillae

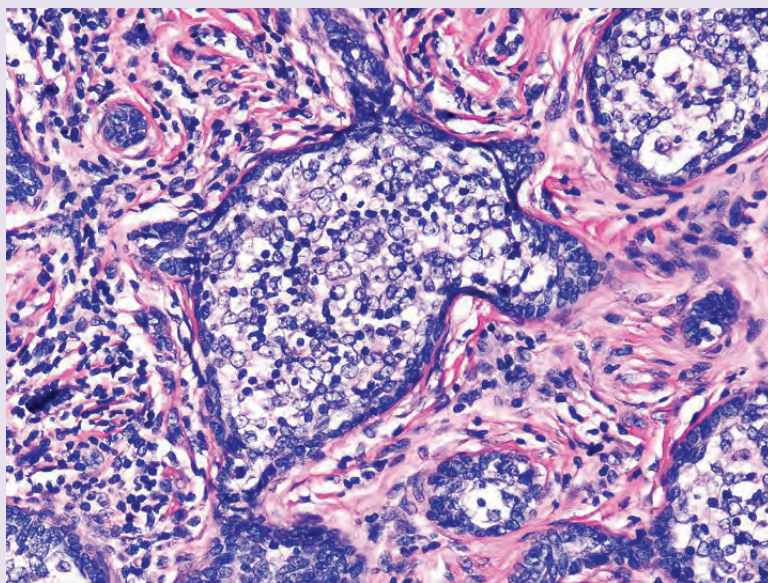


BENIGN NEOPLASMS**Adamantinoid Trichoblastoma (Cutaneous Cystadenoma)**

Well circumscribed tumor with small nodules of basaloid cells and dense stroma

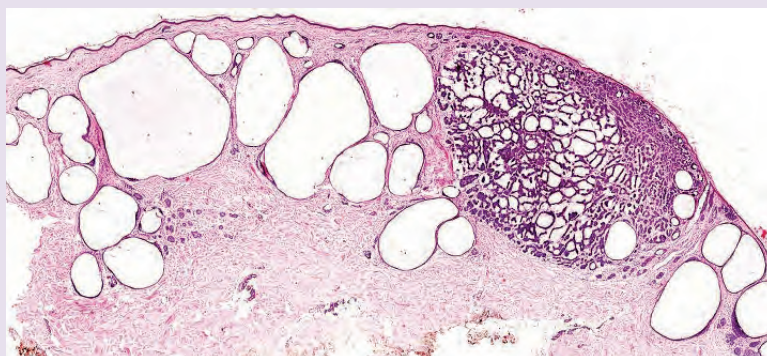


“Pizza sign”: Palisading border, pale center

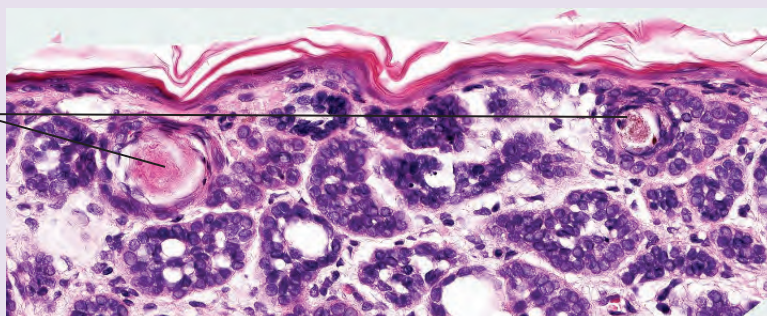


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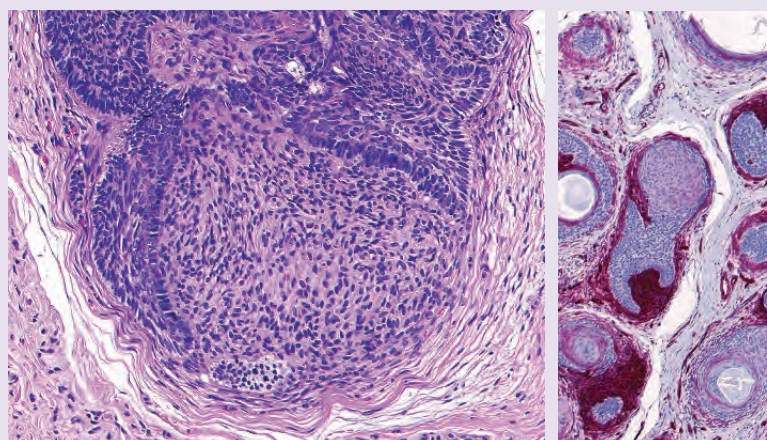
Trichoblastoma, Cystic



Cystic (left) and cribriform (right) growth pattern



Papillary Trichoblastoma



Papillary mesenchymal body in trichoblastoma (left); nestin stain (right)

BENIGN NEOPLASMS

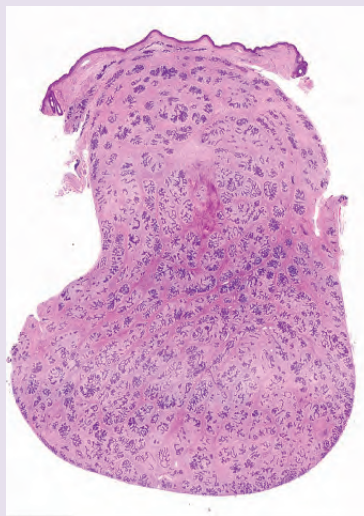
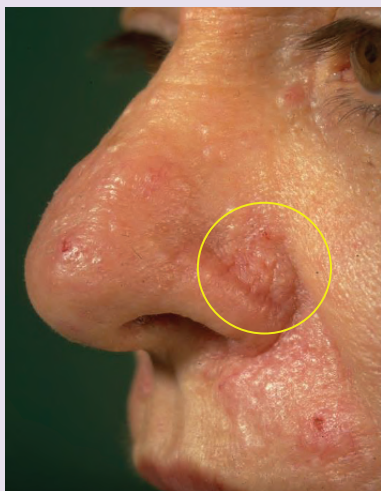
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Trichoepithelioma (Sclerosing Epithelial Hamartoma)

Flat tumor with telangiectases on the nose (left)

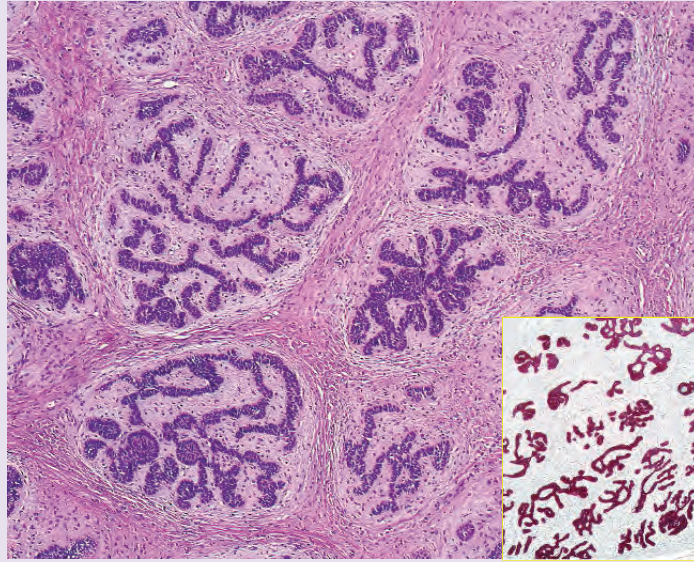
Sclerosing dermal tumor with small strands of basaloid cells (right)



Trichoepithelioma (Sclerosing Epithelial Hamartoma)

Arborising strands of basaloid tumor cells in a densely collagenized stroma

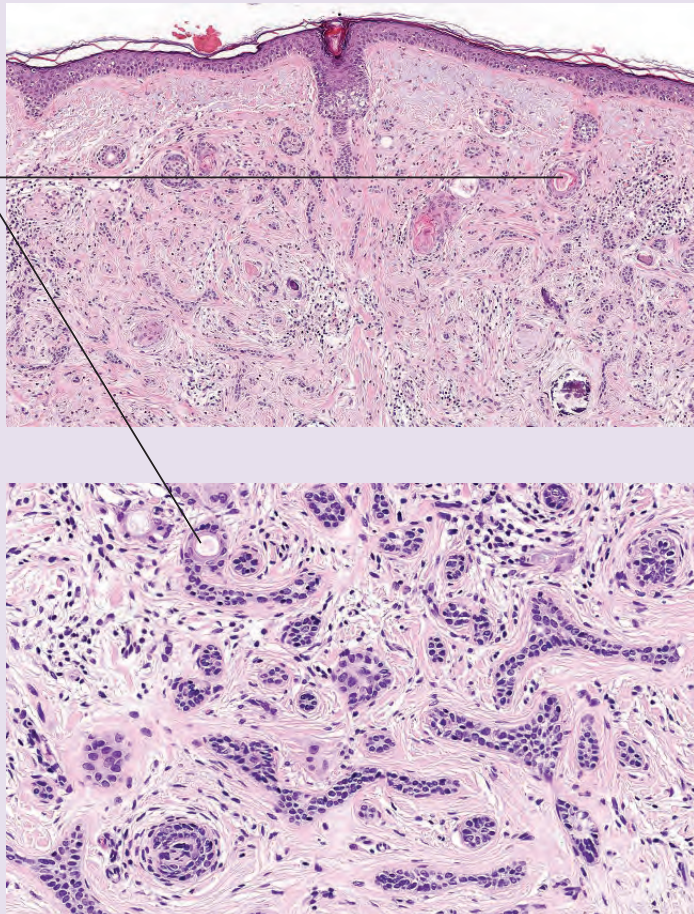
Tumor cells are AE1/AE3 positive (inset)



Desmoplastic Trichoepithelioma (Sclerosing Epithelial Hamartoma)

Foci of follicular keratinization

Branching cords of squamous epithelial cells, embedded in dense collagenous stroma



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Cl: Scar-like, discoid, centrally indented solitary skin-colored tumor with raised borders, preferentially localized in the face of young women.

Hi:

- Symmetrical, poorly circumscribed tumor
- Small cords of squamous epithelium
- Superficial adnexal microcysts
- Dense collagenous paucicellular eosinophilic stroma (desmoplastic variant)

DD: Syringoma; morphea-like basal cell carcinoma; microcystic adnexal carcinoma.

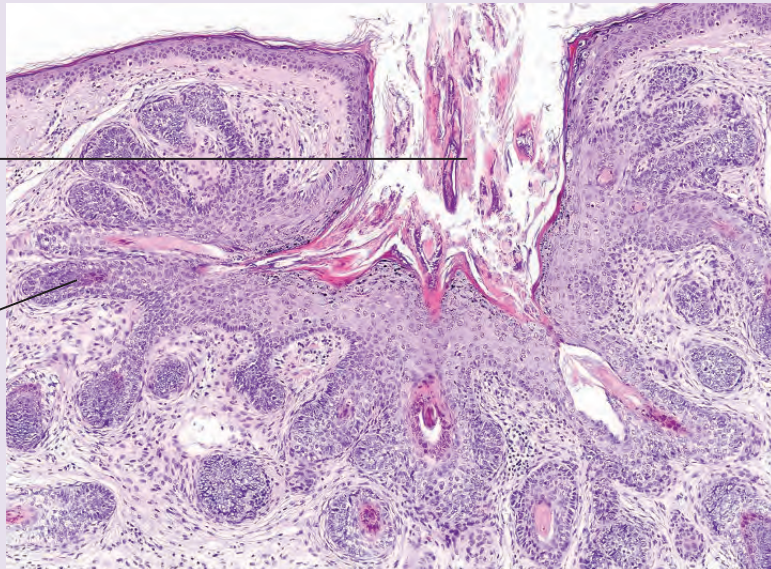
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Trichofolliculoma (Folliculosebaceous Cystic Hamartoma)

Central pore with keratotic material and miniature hair shafts

Radial branching of tiny hair follicles

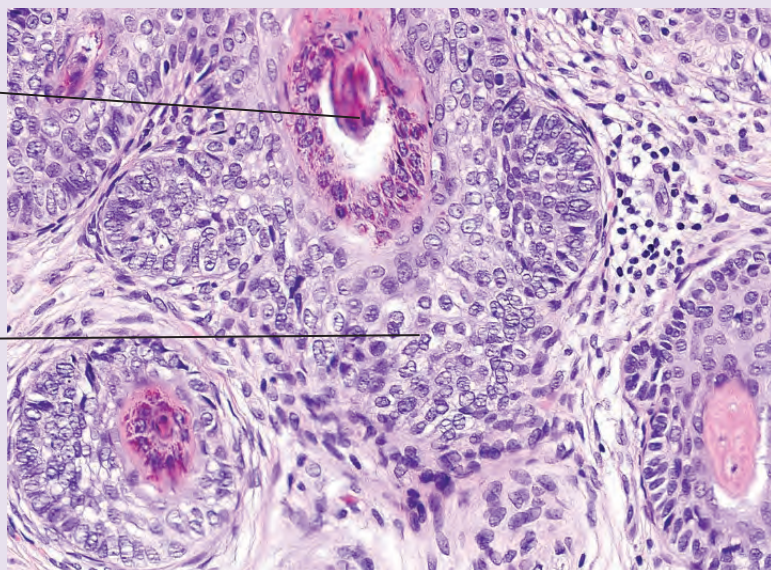


BENIGN NEOPLASMS

Trichofolliculoma (Folliculosebaceous Cystic Hamartoma)

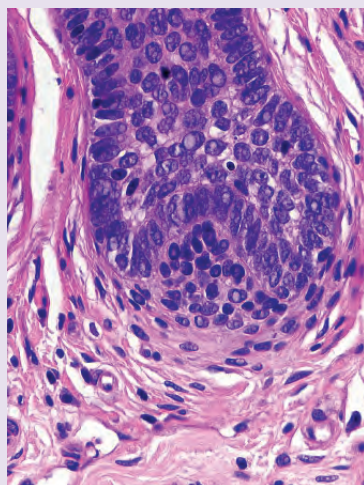
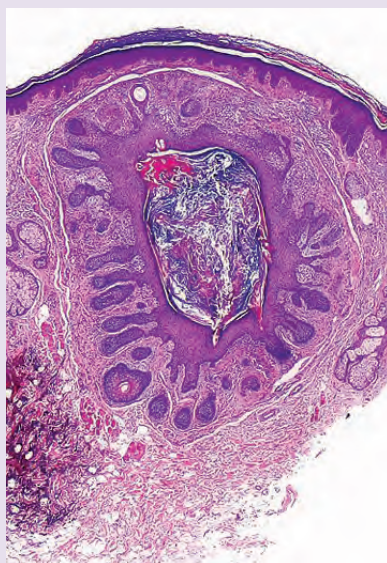
Hair follicles

Clear cells of
the isthmus



Dilated hair
follicle, filled with
keratin and radial
branching of tiny
hair follicles (left)

Hair follicle with
papilla (right)

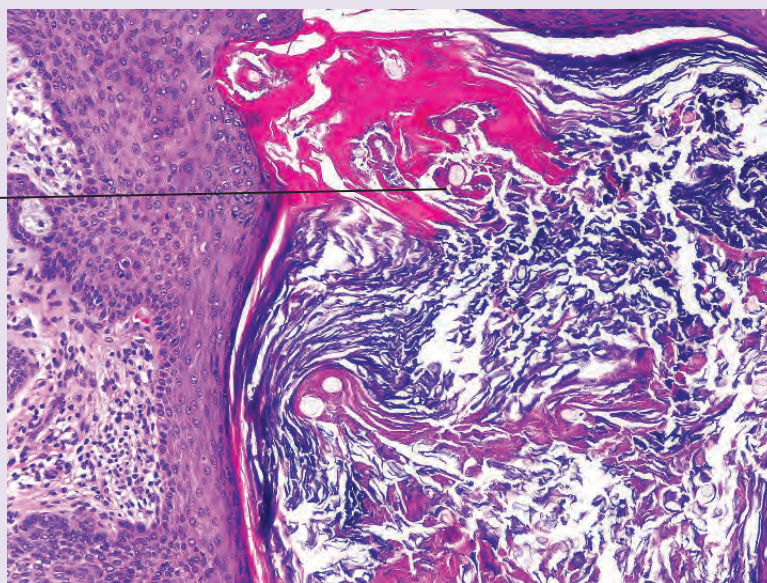


BENIGN NEOPLASMS

Trichofolliculoma (Folliculosebaceous Cystic Hamartoma)

Pseudocystic
border

Vellus hair
within keratotic
mass



CI: Solitary papule preferentially on the nose of adults or in other localisations of the head and neck. Multiple small abortive hair follicles emerge centrifugally from a central horn-filled follicular cystic dilation. Folliculosebaceous cystic hamartoma is considered to be a variant of trichofolliculoma or sebaceous trichofolliculoma with many sebaceous glands.

Hi:

- Dilated and branching follicular structure, opening to the surface
- Abortive small hair follicles branching out from the outer follicular layer
- Branches contain immature and well-differentiated follicles with hair papillae
- Sebaceous differentiation (small lobules) rare

DD: Basal cell carcinoma; trichoepithelioma; fibrofolliculoma.

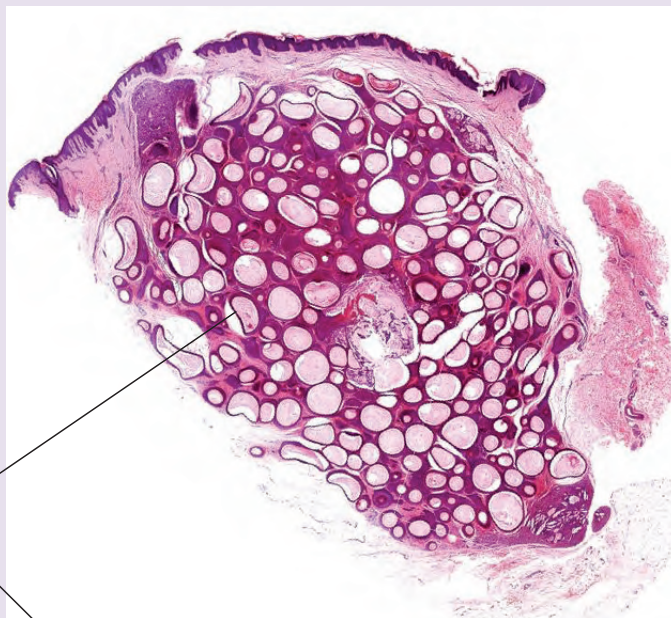
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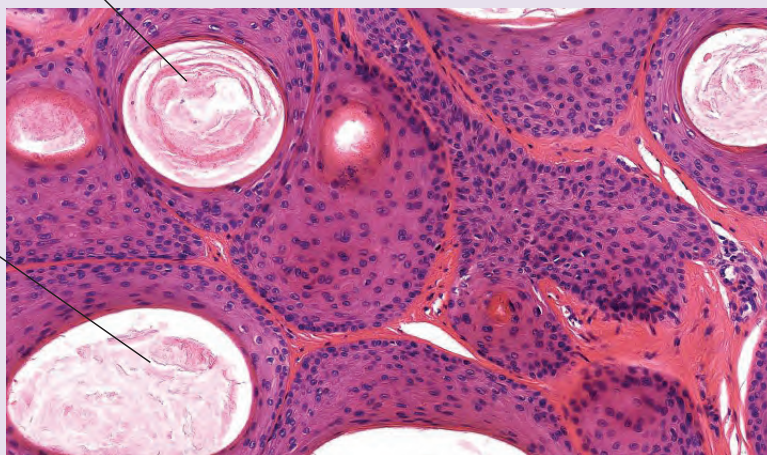
BENIGN NEOPLASMS

Trichoadenoma (Nikolowski)

Interconnecting
follicular
microcysts



Folliculo-cystic
differentiation



Cl: Solitary firm nodule; rare.

Hi:

- Eosinophilic tumor composed of multiple small round follicular horn-filled cysts, interconnected by small epithelial bridges
- No connection with the epidermis
- Granular layer usually absent
- Dense collagenous stroma

DD: Trichoepithelioma; microcystic adnexal carcinoma; basal cell carcinoma.

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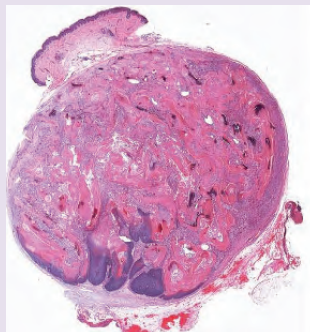
BENIGN NEOPLASMS

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Pilomatricoma (Calcifying Epithelioma Malherbe)

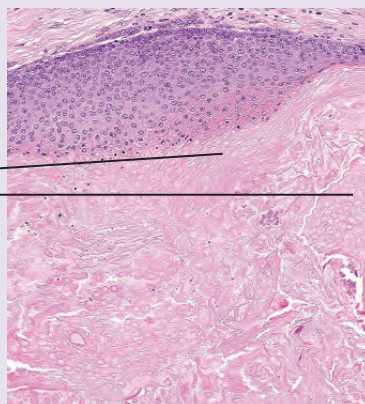
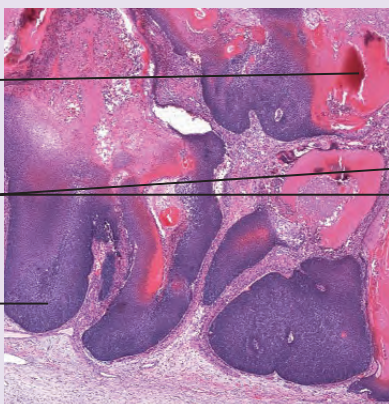
Exophytic growth of firm cutaneous tumor on the arm



Calcification

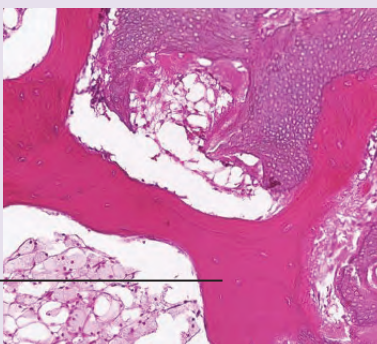
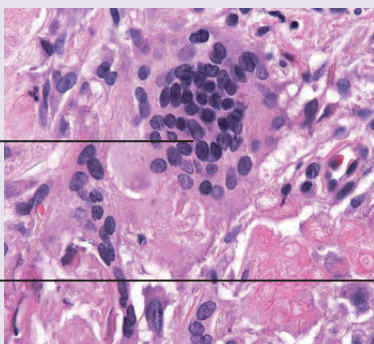
“Shadow” cells

Basaloid matrical cells



Foreign body giant cell

Metaplastic ossification



BENIGN NEOPLASMS

CI: Solitary firm cutaneous or subcutaneous nodule, preferentially on face, upper extremities and shoulder of children, simulating an epidermoid cyst.

Hi:

- Nodular tumor mostly consisting of irregularly shaped lobules of basaloid germinative cells
- Deep basophilic basaloid germinative cells showing differentiation towards hair matrix cells
- Gradual transition from germinative cells to “shadow cells” to necrotic debris
- Metaplastic calcification and ossification may occur
- High proliferative activity with many mitoses
- Inflammatory granulomatous foreign body reaction with multinucleated giant cells

Immunocytochemistry: Characteristic co-expression of high molecular weight cytokeratin and beta-catenin.

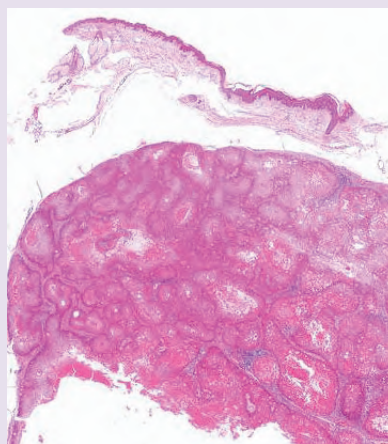
DD: Epidermoid cyst; trichilemmal cyst; trichilemmal carcinoma; squamous cell carcinoma; basal cell carcinoma; pilomatrical carcinoma.

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Proliferating Trichilemmal (Pilar) Tumor (PTT) (Proliferating Trichilemmal Cyst)

Exophytic cutaneous tumor on the back



BENIGN NEOPLASMS

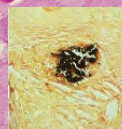
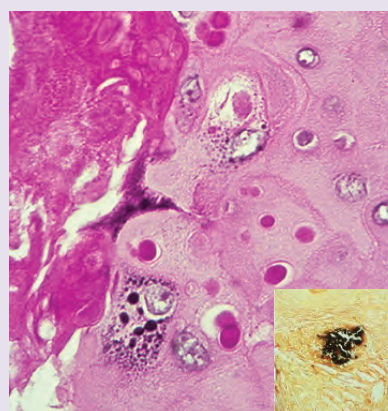
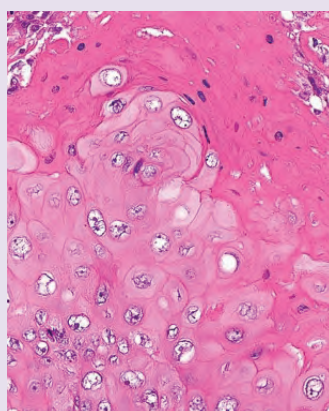
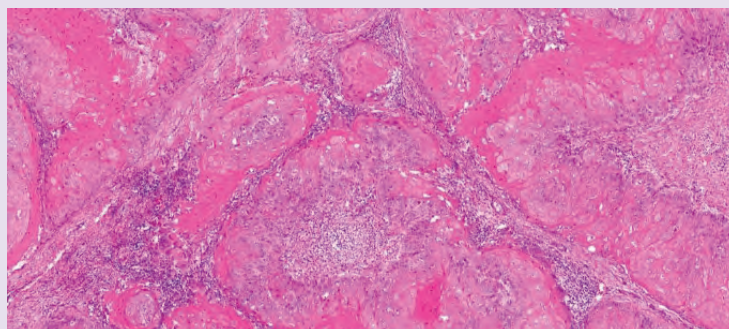
Proliferating Trichilemmal (Pilar) Tumor (PTT) (Proliferating Trichilemmal Cyst)

Sharply circumscribed tumor with smooth outer margin (right top)

Confluent sheets with trichilemmal keratinization (middle)

Squamous epithelium, showing trichilemmal keratinization (left)

Atypical squamous cells, eosinophilic keratotic mass (right). Focal calcification (inset)



Kossa

Cl: Large, dermal or subcutaneous, slowly growing, exophytic tumor on the scalp, sometimes on the back of elderly individuals, arising from pre-existing trichilemmal cyst. Untreated, it may become inflamed and ulcerated. Prognosis usually excellent. Malignant transformation with metastases may occur in exceptionally large lesions.

Hi:

- Sharply circumscribed, partially cystic and lobulated tumor, extending into the subcutis
- Inward-bound lobular growth pattern of cells with trichilemmal keratinization (isthmus-catagen type of epithelia), correlating to trichilemmal cyst
- Irregular lobular architecture suggesting carcinomatous growth, albeit without dysplasia, mitotic activity, and marked necroses
- Proliferative activity (Ki67) limited to the basal zones of individual lobules
- Cystic spaces may be filled with inflammatory infiltrate and amorphous horn masses
- Foci of dystrophic calcification

DD: Trichilemmal cyst; squamous cell carcinoma; trichilemmal carcinoma; pilomatricomas; basal cell carcinomas; epithelioma cuniculatum. Malignant proliferating trichilemmal cyst is the most important differential diagnosis, showing very large size (>5 cm), poor outer circumscription with focal invasive growth, increased mitotic activity – in particular within suprabasal layers and massive central necrosis.

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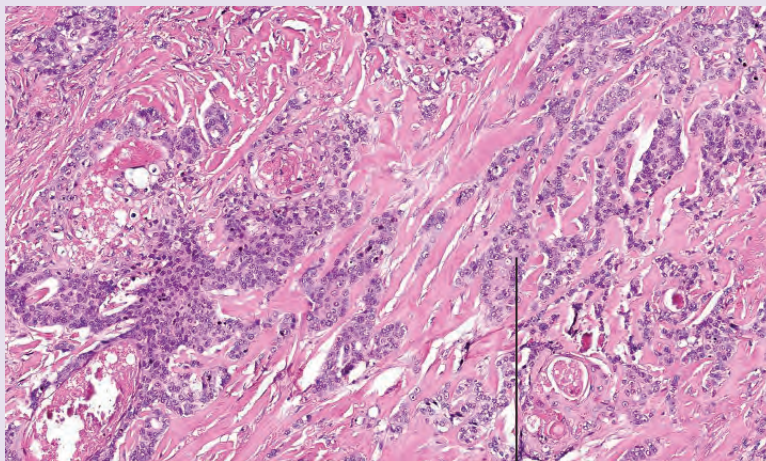
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MALIGNANT NEOPLASMS

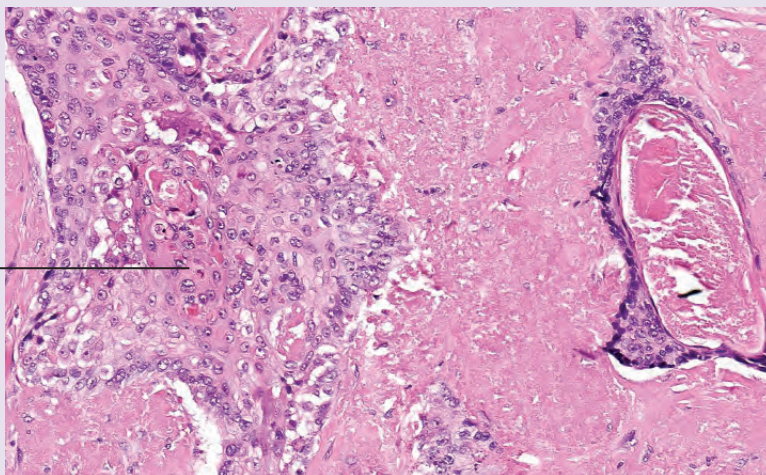
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Malignant Neoplasms

Malignant Pilomatricoma (Pilomatrical Carcinoma)



Infiltrating growth of atypical pilomatrical cells



Focal necrosis.
Prominent lack
of shadow cells

MALIGNANT NEOPLASMS

Cl: Rare malignant variant of pilomatricoma.

Hi:

- Large size (>5 cm)
- Infiltrating growth pattern
- Marked loss of shadow cells – with abrupt transition from germinative cells to necrotic debris

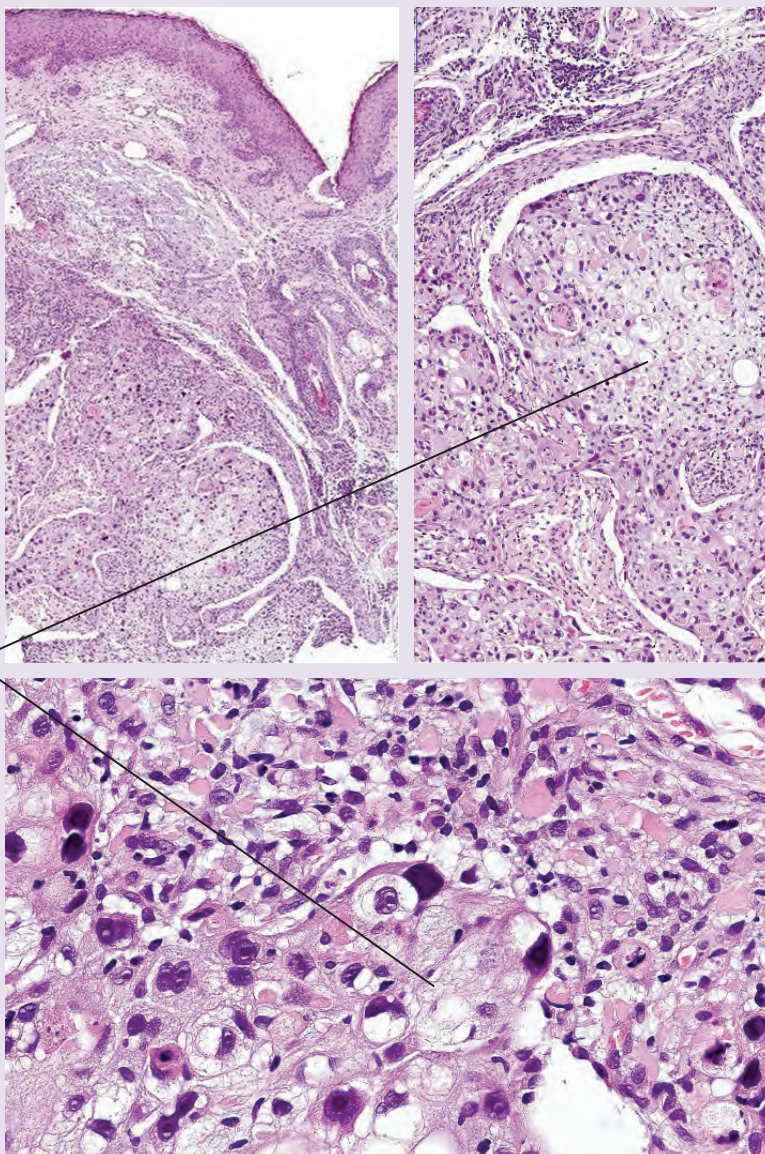
- Hyperchromasia and pleomorphism involving all parts of the tumor
- Many mitoses

DD: Squamous cell carcinoma, pilomatricoma.

Trichilemmal Carcinoma

Proliferation of
pleomorphic
tumor cells

Atypical clear
cells



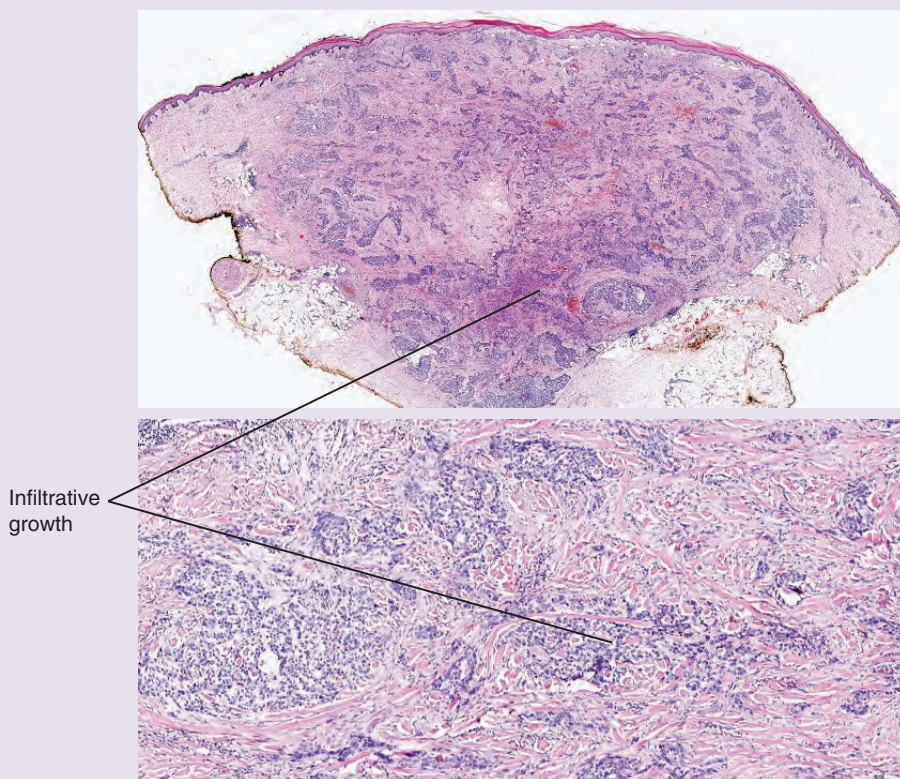
MALIGNANT NEOPLASMS

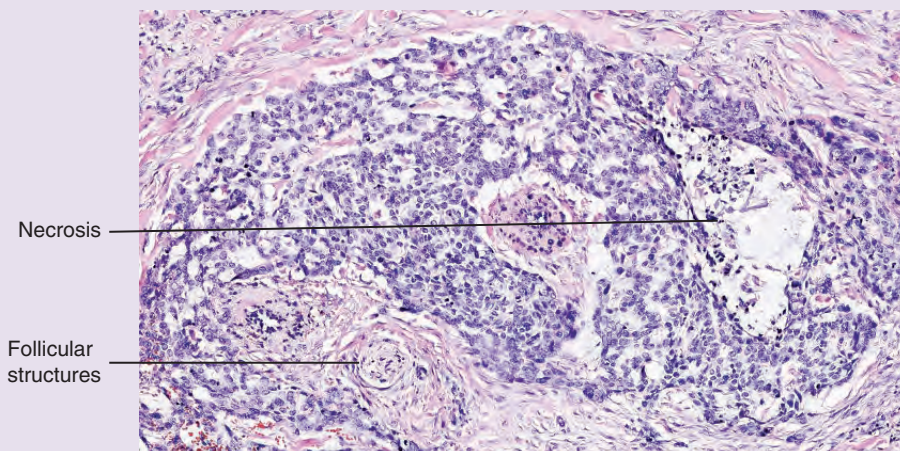
Trichilemmal carcinoma is considered to be a pleomorphic clear cell variant of squamous cell carcinoma showing features of trichilemmal differentiation.

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Trichoblastic Carcinoma



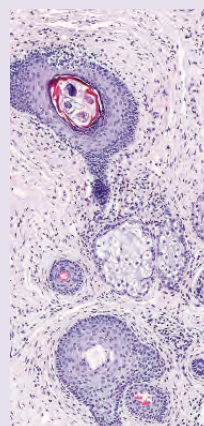
BENIGN NEOPLASM**Trichoblastic Carcinoma**

Trichoblastic carcinoma is the malignant variant of trichoblastoma, which most commonly develops in sebaceous nevus of Jadassohn. Infiltrative growth pattern, cellular atypia and focal necrosis are found.

**Pilosebaceous Mesenchyme
Benign Neoplasm****Trichodiscoma (Follicular Fibroma, Fibrofolliculoma, Perifollicular Fibroma)**

Birt-Hogg-Dubé
syndrome;
forehead (left)

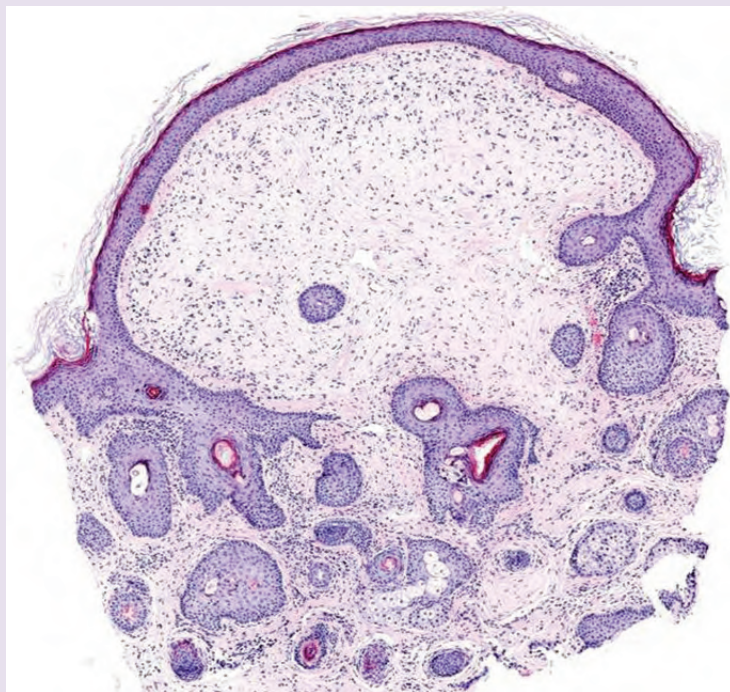
Concentric
periadnexal
stroma



BENIGN NEOPLASM

Spindle Cell Predominant Trichodiscoma (Follicular Fibroma, Fibrofolliculoma, Perifollicular Fibroma)

Dense
fibroblastic
stroma



Cl: Fibrofolliculoma, perifollicular fibroma, and trichodiscoma are proliferations of the dermal perifollicular mesenchyme, and are considered to be different stages of evolution of a single tumor entity that clinically mostly presents with small papules, preferentially in the head and neck area. Trichodiscoma may appear as a sporadic variant with solitary protuberant lesions in the nasolabial area, or as multiple small whitish agminated lesions in the setting of Birt-Hogg-Dubé syndrome (associated with tumors of the kidney and pulmonary cysts).

Hi:

- Exophytic tumor with adnexal (sebaceous) and stromal (fibroblasts) components
- Aggregated and fascicularly oriented CD34-positive fibroblasts with interspersed adipocytes in the center
- Mucin-rich stroma (imitating spindle cell lipoma)
- Hyperplastic sebaceous glands on either side of the tumor
- Mature hair follicle missing; rarely small vellus hair at the outer periphery

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CHAPTER 3

Paget's Disease

CHAPTER MENU

Mammary Paget's Disease

Extramammary Paget's Disease

Mammary Paget's Disease

Cl: Eczema-like or psoriasiform or bowenoid lesions unilaterally in or around one nipple of the breast, mostly in females. They reflect intraepidermal metastasis of ductal adenocarcinoma of the breast.

Hi:

- Intraepidermal pagetoid spread of large clear cells with pale cytoplasm and prominent nucleus
- All epidermal layers favored, in contrast to superficial spreading melanoma, in which the basal layer is favored

- Cells are positive for PAS and CK7, EMA, and CAM5.2
- Small amounts of mucin
- Lack of dyskeratosis
- Superficial erosion, covered with crust
- Increased number of melanocytes may occur

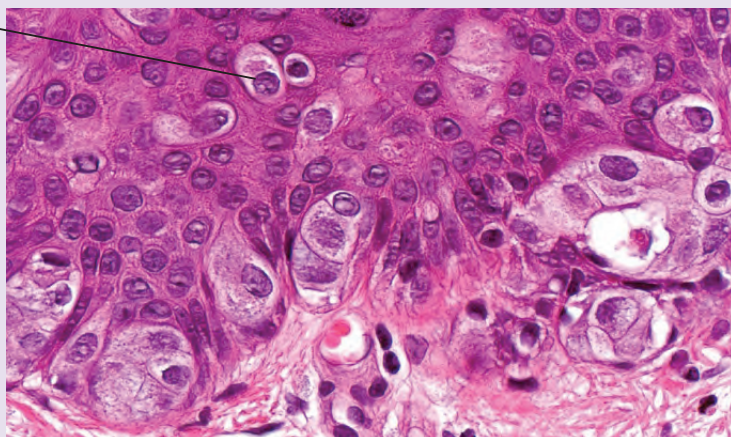
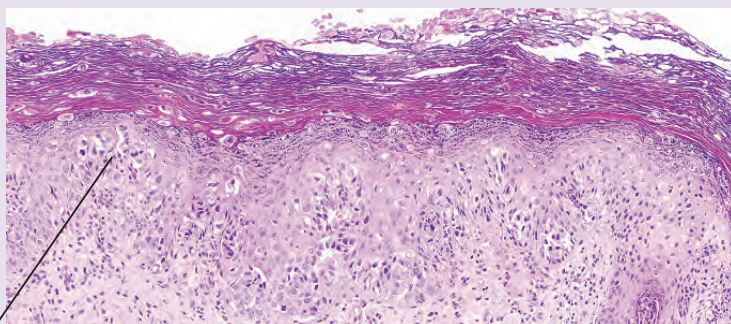
DD: Pagetoid melanoma (S100; melanoma-specific markers); Bowen's disease; pagetoid reticulosis. Toker cells (CK7+) are regular non-neoplastic autochthonous intraepidermal clear cells, which are found in 10% of normal nipple epidermis.

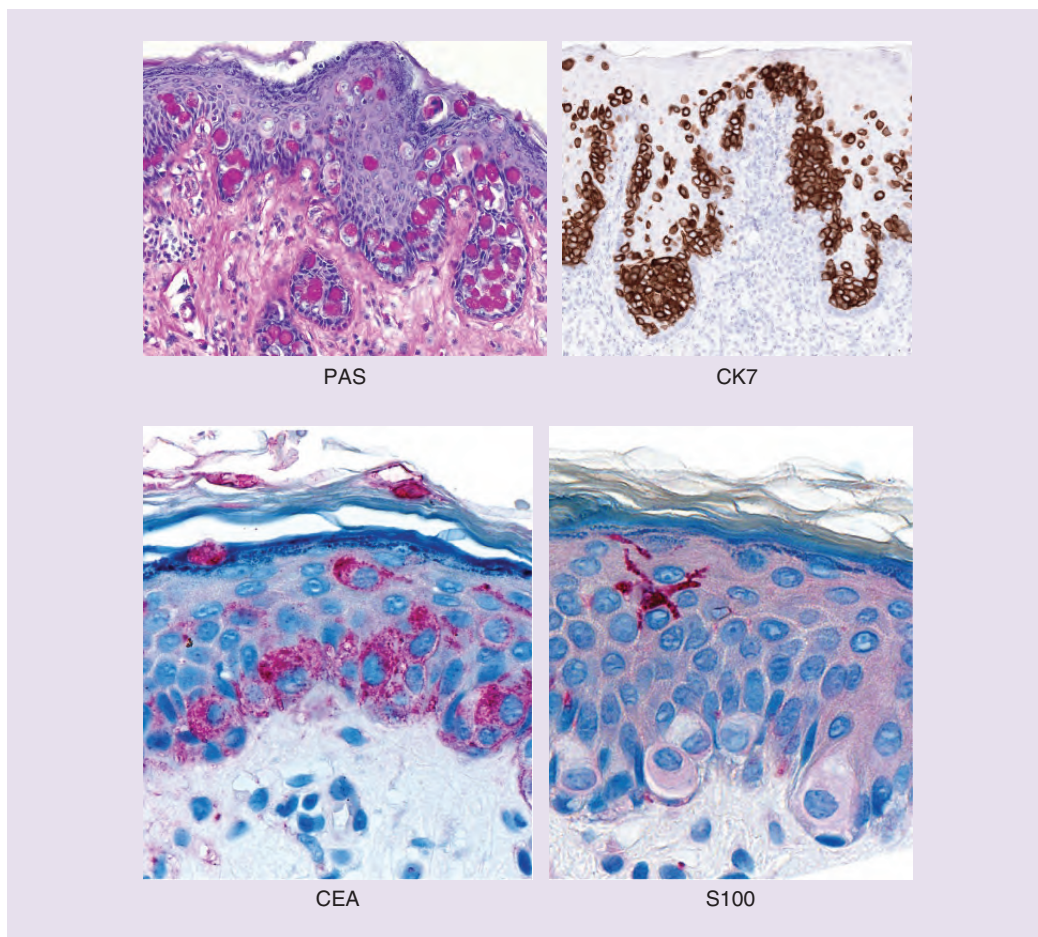
Extramammary Paget's Disease

Mammary and extramammary Paget's disease: eczematous, psoriasiform lesions



Pale tumor cells in all levels of the epidermis ("pagetoid pattern")





More than 20% of these are associated with visceral malignancies of the GU or GI tract.

Cl: Scaling eczematous or psoriasiform lesions in the anogenital region, axilla or other areas with apocrine glands. Oozing and crust formation.

Hi: Similar to mammary Paget. PAS-positive tumor cells within all layers of the epidermis and within follicular epithelium.

DD: Superficial spreading melanoma; Bowen's disease; pagetoid reticulosis; apocrine carcinoma of the groin with intraepidermal pagetoid dissemination; metastasizing urothelial and vesicular carcinoma (uropapkin-positive); rectal and colon carcinoma (CDX2-positive); prostate carcinoma (PSA-positive).

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- Petersson, E., Ivan, D., Kazakov, D.V., Michal, M., and Prieto, V.G. (2009) Pigmented Paget disease – a diagnostic pitfall mimicking melanoma. *Am J Dermatopathol* **31**(3): 223–6.
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CHAPTER 4

Melanocytes

CHAPTER MENU

Non-Neoplastic Hyperpigmentations	Blue Nevii
Ephelides (Genuine Freckles)	Dermal Melanocytosis
PUVA (Psoralen UVA) Lentigo	Spindle and/or Epithelioid Cell Nevus
“Nevus” Spilus (Speckled Lentiginous Nevus; Café-Au-Lait Spot)	Benign Melanocytic Lesions with Peculiar Structural Features
“Ink” Spot Lentigo (Reticulated Melanocytic Macule)	Malignant Melanocytic Neoplasms
Senile Freckles (Solar [Actinic] Lentigo)	Lentigo Maligna Dubreuilh (Hutchinson’s Freckle)
Mucosal Lentiginous Spots (Lip, Buccal, and Genital Mucosa)	Malignant Melanoma
Nevi	Common Clinical Differential Diagnoses of Malignant Melanoma
Common Acquired Melanocytic Nevii	

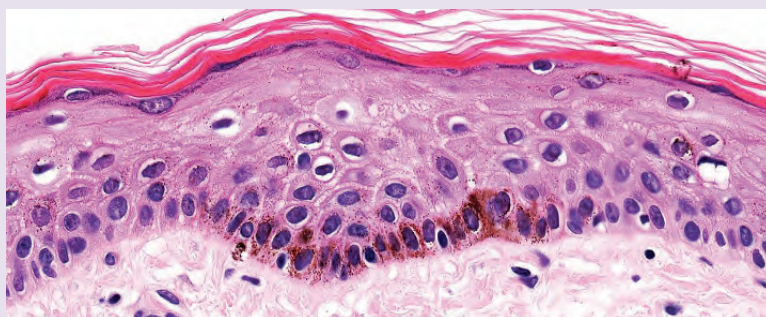
Non-Neoplastic Hyperpigmentations

Ephelides (Genuine Freckles)

Genuine
ephelides



Focal basal
hyperpigmentation



Cl: Small brown roundish macules, preferentially in sun-exposed areas of the face and shoulders in fair-skinned individuals (Fitzpatrick type I or II). Genetic predisposition.

Hi: Focal hyperpigmentation of the epidermal basal layer. The number of melanocytes is normal.

DD: Café-au-lait spots; syndromic melanotic macules; ink spot; actinic lentigo.

References

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- Rhodes, A.R., Albert, L.S., Barnhill, R.L., and Weinstock, M.A. (1991) Sun-induced freckles in children and young adults. A correlation of clinical and histopathologic features. *Cancer* **67**(7): 1990–2001.

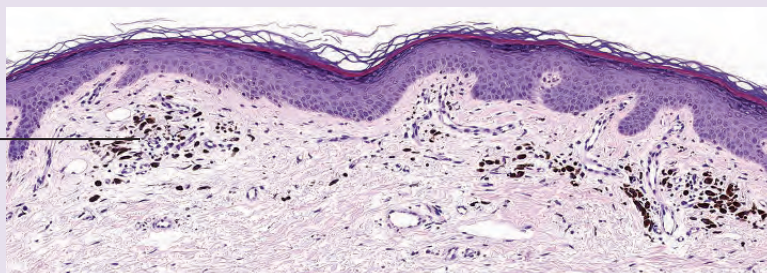
PUVA (Psoralen UVA) Lentigo

PUVA-
ephelides



PUVA (Psoralen UVA) Lentigo

Melanophages
in the dermis



Cl: Small light-brown splash-like macules resulting from long-lasting therapy with psoralen and UVA (PUVA).

Hi: Hyperpigmented melanophages in the upper dermis.

References

- Kanerva, L., Niemi, K.M., and Lauharanta, J. (1984). A semiquantitative light and electron microscopic analysis of histopathologic changes in photochemotherapy-induced freckles. *Arch Dermatol Res* **276**(1): 2–11.
- Kanerva, L., Lauharanta, J., Niemi, K.M., Juvakoski, T., and Lassus, A. (1983) Persistent ashen-gray maculae and freckles induced by long-term PUVA treatment. *Dermatologica* **166**(6): 281–6.

“Nevus” Spilus (Speckled Lentiginous Nevus; Café-Au-Lait Spot)

Nevus spilus
(left)

Ink spot (right)

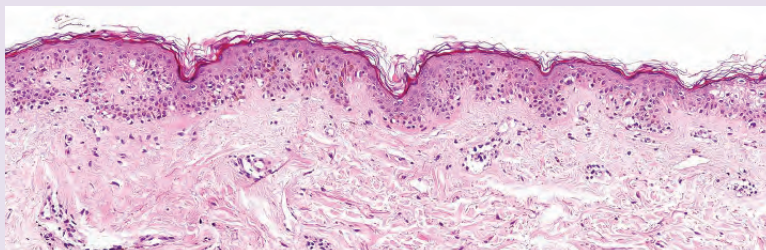


“Ink-Spot” Lentigo (Reticulated Melanocytic Macule)



“Nevus” Spilus

Slight acanthosis,
melanocytes and
pigment loaded
keratinocytes



Cl: Widespread or segmental macules of variable size and uniform light-brown color, usually persisting from birth throughout life without change. There may be multiple disseminated hyperpigmented spots (melanocytic nevi of various sizes) within the macule. Melanoma arising in a nevus spilus has been reported.

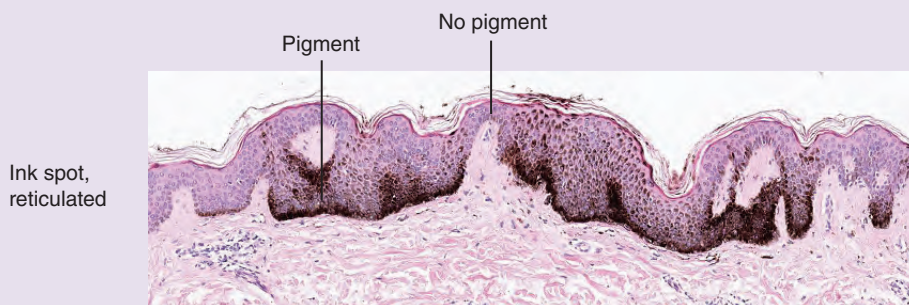
Hi:

- Slight acanthosis with elongated rete ridges
- Melanin in keratinocytes
- Slight increase of the number of melanocytes
- Within the lentiginous zone, multiple interspersed nevi (junctional, compound, large congenital) of various sizes may be present

References

- Haenssle, H.A., Kaune, K.M., Buhl, T., et al. (2009) Melanoma arising in segmental nevus spilus: detection by sequential digital dermatoscopy. *J Am Acad Dermatol* **61**(2): 337–41.
- Kurban, R.S., Preffer, F.I., Sober, A.J., Mihm, M.C. Jr, and Barnhill, R.L. (1992) Occurrence of melanoma in “dysplastic” nevus spilus: report of case and analysis by flow cytometry. *J Cutan Pathol* **19**(5): 423–8.
- Tavoloni Braga, J.C., Gomes, E., Macedo, M.P., et al. (2014) Early detection of melanoma arising within nevus spilus. *J Am Acad Dermatol* **70**(2): e31–2.
- Torres, K.G., Carle, L., and Royer, M. (2017) Nevus spilus (speckled lentiginous nevus) in the oral cavity: report of a case and review of the literature. *Am J Dermatopathol* **39**(1): e8–12.

“Ink” Spot Lentigo (Reticulated Melanocytic Macule)



Cl: Small black bizarre spot with jagged borders (“black splash”), mostly in sun-exposed areas of adults.

Hi:

- Heavy hyperpigmentation of the epidermis, particularly at the tips of rete ridges
- Minimal increase of number of melanocytes

- Prominent hypopigmented skip zones between hyperpigmented rete ridges

Reference

- Bolognia, J.L. (1992) Reticulated black solar lentigo (‘ink spot’ lentigo). *Arch Dermatol* **128**(7): 934–40.

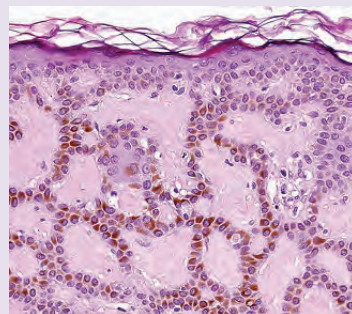
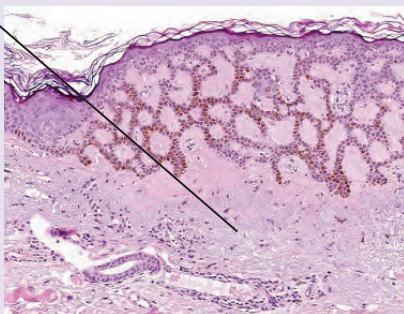
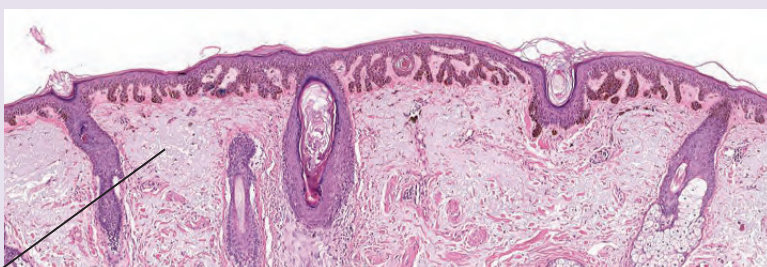
Senile Freckles (Solar [Actinic] Lentigo)

Lentiginous spots
on the back of
the hand



Bud-like
elongated rete
ridges with basal
hyperpigmen-
tation
("dirty feet")

Solar elastosis



Pseudopod-like epidermal proliferations with hyperpigmentation

Cl: These common flat, pigmented lesions, preferentially located in sun-exposed areas of elderly individuals, are considered to be flat seborrheic keratosis.

Hi:

- Elongated pseudopod-like projections and lentiginous proliferation of rete ridges

- Increased pigment in keratinocytes at base of rete ridges ("dirty feet" sign)
- Number of melanocytes normal or slightly increased
- Solar elastosis in the upper dermis

DD: Lentigo maligna, other pigmented lentiginous lesions.

References

- Black, W.H., Thareja, S.K., Blake, B.P., Chen, R., Cherpelis, B.S., and Glass, L.F. (2011) Distinction of melanoma in situ from solar lentigo on sun-damaged skin using morphometrics and MITF immunohistochemistry. *Am J Dermatopathol* **33**(6): 573–8.
- Feinmesser, M., Tsabari, C., Fichman, S., Hodak, E., Sulkes, J., and Okon, E. (2003) Differential expression of proliferation- and apoptosis-related markers in lentigo maligna and solar keratosis keratinocytes. *Am J Dermatopathol* **25**(4): 300–7.
- Fraga, G.R. and Amin, S.M. (2014) Large cell acanthoma: a variant of solar lentigo with cellular hypertrophy. *J Cutan Pathol* **41**(9): 733–9.
- Hillesheim, P.B., Slone, S., Kelley, D., Malone, J., and Bahrami, S. (2011) An immunohistochemical comparison between MITF and MART-1 with Azure blue counterstaining in the setting of solar lentigo and melanoma in situ. *J Cutan Pathol* **38**(7): 565–9.
- Sethi, M., Craythorne, E., Al-Arashi, M.Y., Bhawan, J., and Stefanato, C.M. (2014) Macromelanosomes: their significantly greater presence in the margins of a lentigo maligna versus solar lentigo. *Am J Dermatopathol* **36**(6): 490–2.

Mucosal Lentiginous Spots (Lip, Buccal, and Genital Mucosa)

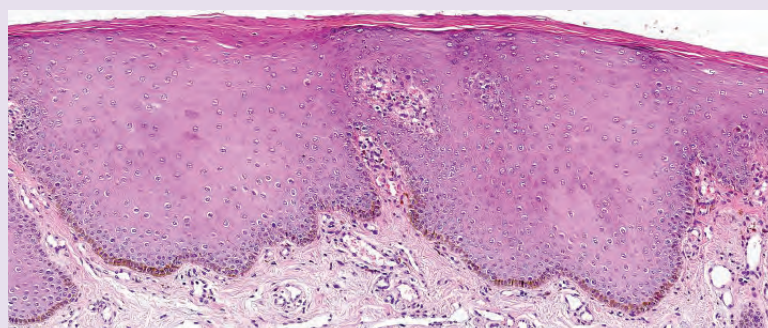
Gingiva



Labial lentigo



Basal hyperpigmentation



COMMON ACQUIRED MELANOCYTIC NEVI

CI: These lesions may be solitary or syndromic (Peutz–Jeghers syndrome; Laugier–Hunzinger syndrome).

Hi:

- Regular mucosa
- Basal hyperpigmentation
- No significant increase of number of melanocytes

DD: Incipient mucosal melanoma: increased number of irregularly spaced single melanocytes in the basal zone (“mycosis fungoides” pattern).

Nevi

Common Acquired Melanocytic Nevi

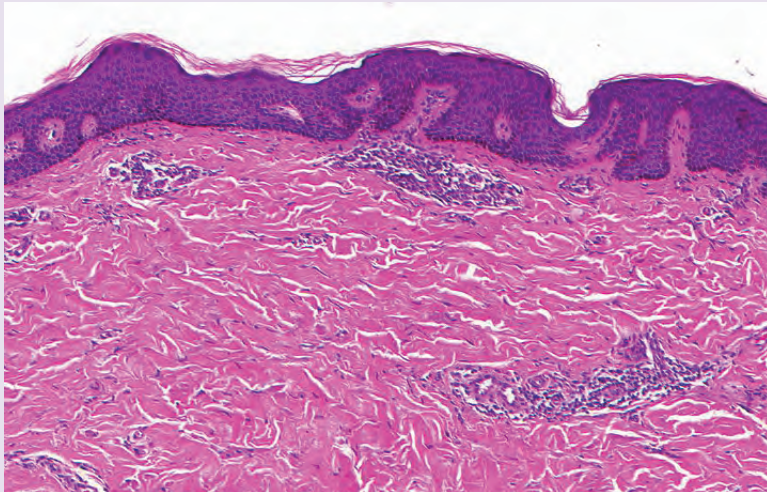
Melanosis Neviformis (Pigmented Hairy Epidermal Nevus; Becker Nevus)

Hairless (left) and hairy (right) pigmented nevi



Acanthosis with basal hyperpigmentation

“Flat bottom” rete tips



CI: Even though the lesions exist from birth, they become apparent mostly in puberty as slightly hyperpigmented, irregular but sharply demarcated macules with growth of terminal hairs. Back and shoulder are favored sites.

Hi:

- Elongation of rete ridges with characteristic “flat bottom” rete tips throughout the lesion
- Normal number of melanocytes
- Melanin in basal keratinocytes
- Increased number of hair follicles and bundles of smooth muscle in the dermis

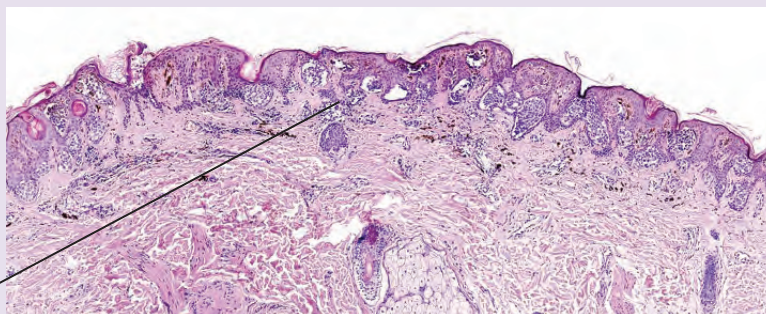
COMMON ACQUIRED MELANOCYTIC NEVI

Junctional Nevus

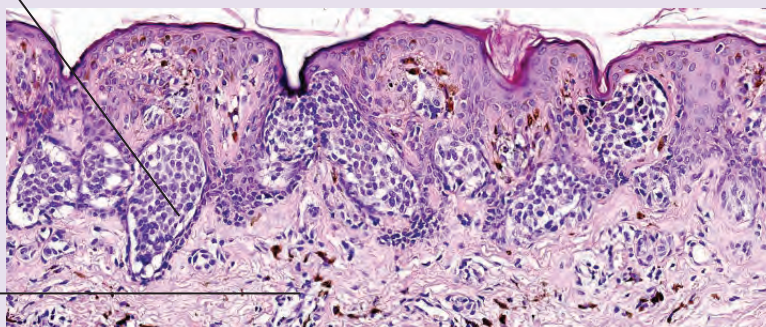
Flat reddish-brown pigmented lesion



Clusters and nests of melanocytes in the lower part of the epidermis and at the junction



Melanophages



Cl: Flat or slightly raised, pigmented macule; blurred border. Initial forms are referred to as lentigo simplex or even “jentigo” (junctional nevus/lentigo).

Hi:

- Melanocytes in single clusters and in nests
- Restricted to the lower part of the epidermis and the dermoepidermal junction
- Lateral borders (“shoulder”) taper out with small peripheral nests

- No melanocytic atypia
- No melanocytes within the dermis
- Melanophages are often present
- Slight lymphocytic infiltrate may be present in the upper dermis

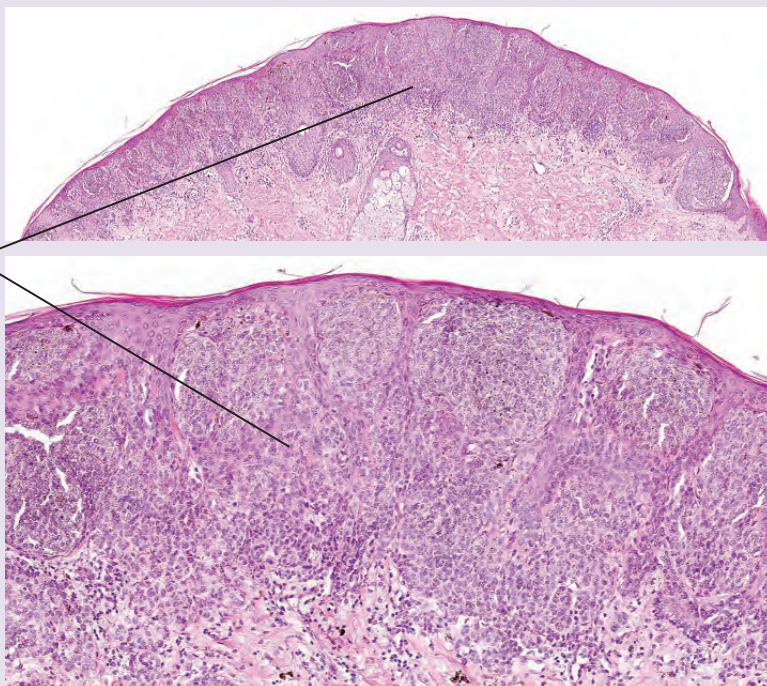
DD: Activated or proliferating junctional nevus, showing compact horny layer, replete with melanin granules, melanocytic activity at the base, broad band of melanophages and inflammatory infiltrate in the upper dermis.

COMMON ACQUIRED MELANOCYTIC NEVI**Compound Nevus**

Compound nevi



Nests of melanocytes at the dermo-epidermal junction and in the upper dermis



Cl: Mostly pigmented papules of variable size, sometimes hairy.

Hi:

- Symmetrical melanocytic lesion with sharp borders
- Junctional part: intraepidermal nests of melanocytes
- Dermal part: dermal nests of melanocytes
- Broad papillae, filled with melanocytes
- Elongated rete ridges
- No single melanocytes above the basal layer

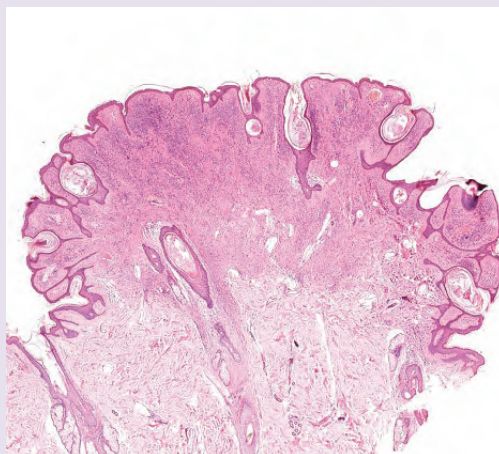
COMMON ACQUIRED MELANOCYTIC NEVI

Comment: Nevi on palms or soles (acral nevi) can have some melanocytes and pigment scattered intraepidermally. There may be transepidermal elimination of pigment and cells in these special localisations. MANIAC (melanocytic acral nevus

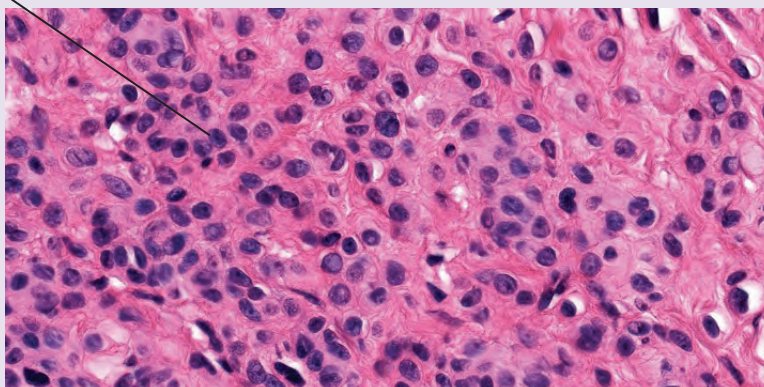
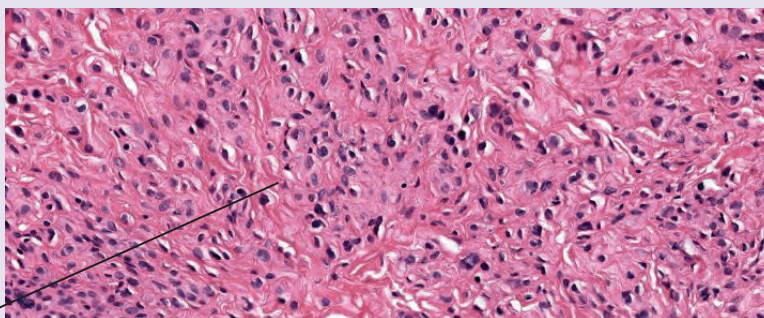
with intraepidermal ascent of cells) is considered to be a melanoma impostor due to small melanocytic nests with transepidermal elimination. Overall features of MANIAC, however, are those of a dysplastic compound nevus in acral skin.

Dermal Nevus

Amelanotic dermal nevus

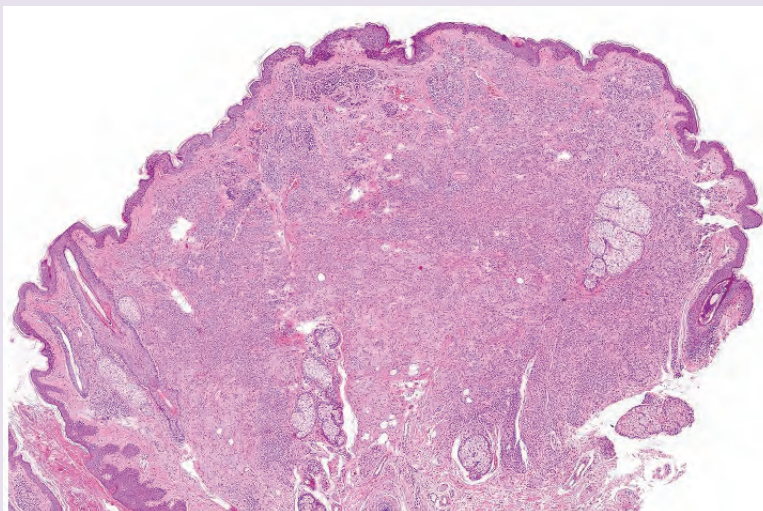


Densely packed melanocytes without cellular atypia

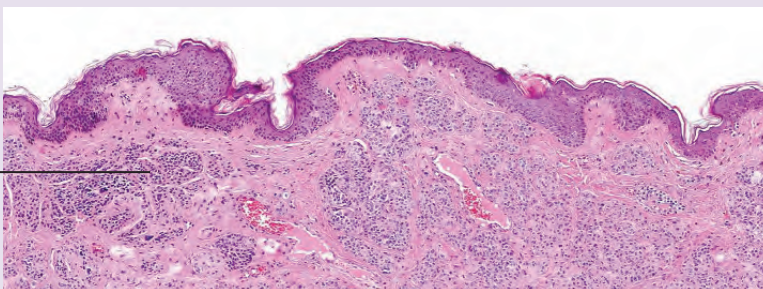
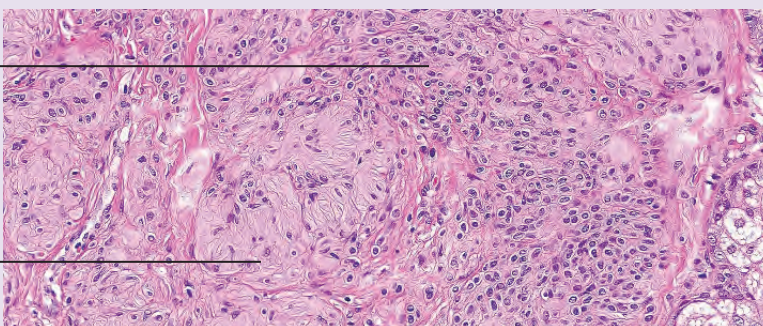


COMMON ACQUIRED MELANOCYTIC NEVI**Dermal Nevus, with Maturation**

Dermal nevus



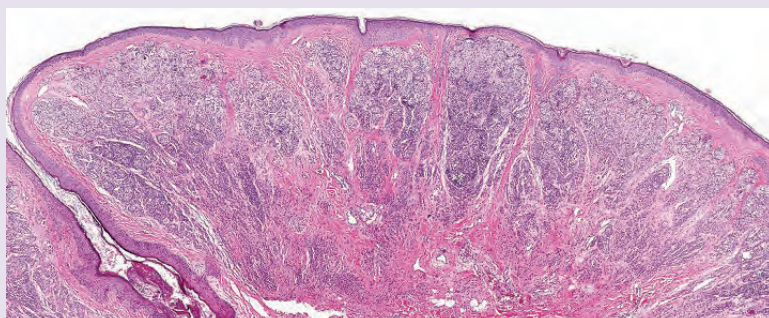
Cuboidal melanocytes

Banal
("lymphoid")
melanocytesType C
("neuroid")
melanocytes

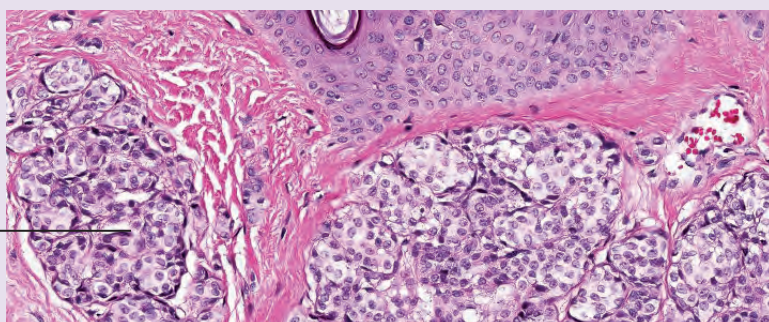
COMMON ACQUIRED MELANOCYTIC NEVI

Dermal Nevus, with Maturation

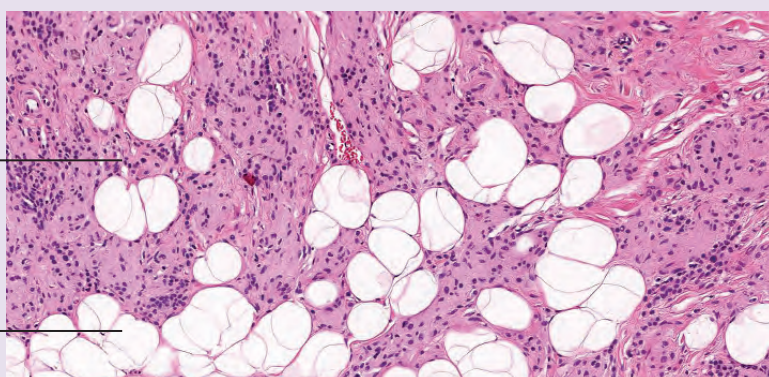
Dermal nevus



Nests of large cuboidal melanocytes



Maturation: Smaller melanocytes some of which show "neural" maturation



Metaplastic lipocytes

Cl: Papule, variably pigmented or amelanotic and skin-colored.

Hi:

- Nests and sheets of densely packed melanocytes within the dermis
- Melanocytes show well-defined cytoplasm; nuclei are roundish or oval with fine chromatin
- Multinuclear melanocytes are sometimes found
- The amount of melanin is variable

Comment: Dermal melanocytes "mature" (i.e. get smaller) when descending from upper dermal levels to deeper layers; large melanocytes eventually may evolve into smaller cells with roundish or epithelioid, sometimes even neuroid cell-like morphology (type C melanocytes).

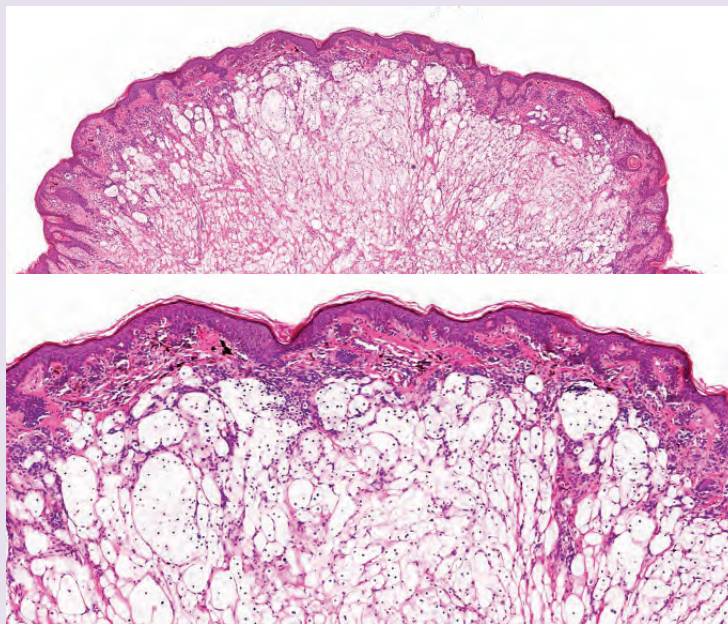
Variant: Miescher's Nevus (Dermal Nevus)

Cl: Clinical variant, showing a broad-based skin-colored nodular lesion, usually on the face, head, and neck.

COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Balloon Cell Nevus

Nests of
"ballooned"
vacuolated
melanocytes
in the dermis



Cl: Histological variant of a melanocytic nevus.

Hi:

- Symmetry and sharp borders as in common melanocytic nevus
- The hallmarks are well-circumscribed nests and clusters of large melanocytes with pale cytoplasm
- Small, peripherally localized multinuclear balloon giant cells are frequently seen

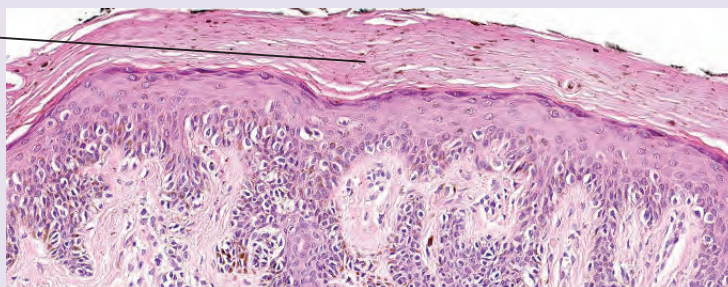
References

- Chiang, Y.Y., Tsai, H.H., Lee, W.R., and Wang, K.H. (2009) Clear cell fibrous papule: report of a case mimicking a balloon cell nevus. *J Cutan Pathol* **36**(3): 381–4.
- Huang, Y.Y. and Vandergriff, T. (2017) Balloon cell change in common blue nevus. *J Cutan Pathol* **44**(4): 407–9.
- McGowan, J.W., Smith, M.K., Ryan, M., and Hood, A.F. (2006) Proliferative nodules with balloon-cell change in a large congenital melanocytic nevus. *J Cutan Pathol* **33**(3): 253–5.
- Urso, C. (2008) Nodal melanocytic nevus with balloon-cell change (nodal balloon-cell nevus). *J Cutan Pathol* **35**(7): 672–6.

Variant: "Activated" Acral (Lentiginous) Melanocytic Nevus

Columns of
pigment in
the compact
cornified layer

Marked
proliferation of
large isomorphic
melanocytes
in the basal layer.
Only minimal
transepidermal
elimination of
single cells



COMMON ACQUIRED MELANOCYTIC NEVI

CI: The hairless skin of palms and soles with thick horny layers are favored sites.

Hi:

- Histological features of junctional nevus
- Sharp borders
- Narrow columns of pigment in the cornified layer
- In early lesions, only a few single melanocytes may be encountered above the basal layer. However, pagetoid spread of melanocytes is not a feature of acral nevus

DD: Acral lentiginous melanoma: increased numbers of irregularly spaced, single melanocytes in the basal layer without accompanying nest

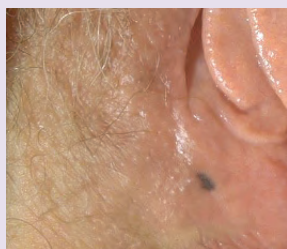
formation usually heralds early acrolentiginous melanoma *in situ* (mycosis fungoides-like pattern of early acrolentiginous melanoma). Intracorneal thrombotic deposits (“black heel”) are a common clinical impostor of atypical melanocytic proliferation at palms and soles.

Reference

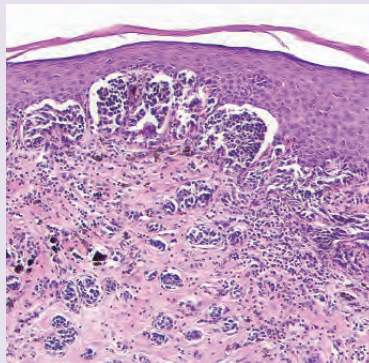
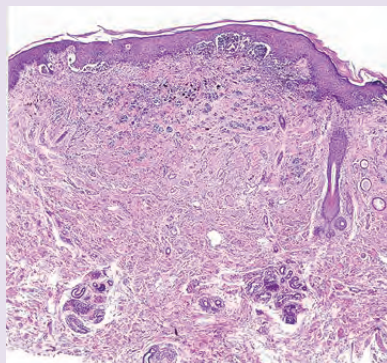
- Saida, T., Koga, H., Goto, Y., and Uhara, H. (2011) Characteristic distribution of melanin columns in the cornified layer of acquired acral nevus: an important clue for histopathologic differentiation from early acral melanoma. *Am J Dermatopathol* 33(5): 468–73.

Variant: (Atypical) Genital Melanocytic Nevus

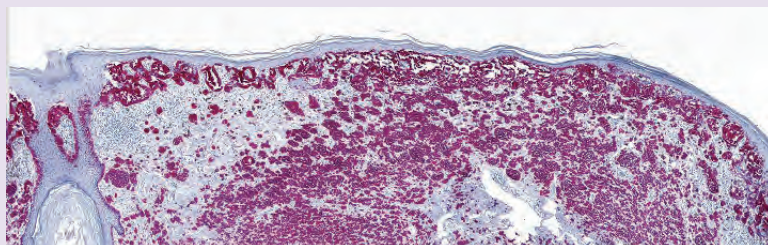
Labia major:
pigmented spots



Dyscohesive
junctional nests
of melanocytes



Compound
nevus. Melan A



COMMON ACQUIRED MELANOCYTIC NEVI

Cl: Mostly flat, clinically “atypical” lesions of the vulva, present in up to 5% of women.

Hi:

- Well-circumscribed symmetrical lesions
- Junctional or compound features
- Enlarged junctional nests of melanocytes
- Intraepidermal (pagetoid) melanocytes
- Slight cytological atypia

DD: Melanoma; epithelioid cell nevus (Spitz).

References

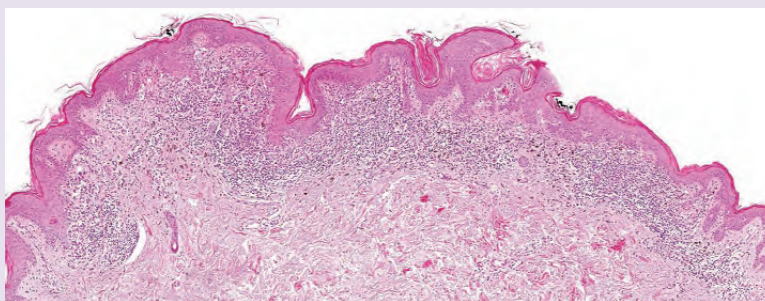
- Brenn, T. (2011) Atypical genital nevus. *Arch Pathol Lab Med* **135**(3): 317–20.
- Hunt, R.D., Orlow, S.J., and Schaffer, J.V. (2014) Genital melanocytic nevi in children: experience in a pediatric dermatology practice. *J Am Acad Dermatol* **70**(3): 429–34.
- Pinto, A., McLaren, S.H., Poppas, D.P., and Magro, C.M. (2012) Genital melanocytic nevus arising in a background of lichen sclerosis in a 7-year-old female: the diagnostic pitfall with malignant melanoma. A literature review. *Am J Dermatopathol* **34**(8): 838–43.
- Polat, M., Topcuoglu, M.A., Tahtaci, Y., Hapa, A., and Yilmaz, F. (2009) Spitz nevus of the genital mucosa. *Indian J Dermatol Venereol Leprol* **75**(2): 167–9.
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- Tseng, D., Kim, J., Warrick, A., et al. (2014) Oncogenic mutations in melanomas and benign melanocytic nevi of the female genital tract. *J Am Acad Dermatol* **71**(2): 229–36.

Variant: Halo Nevus (Leukoderma Centrifugum Acquisitum; Sutton Nevus)

Depigmentation
around
compound nevi



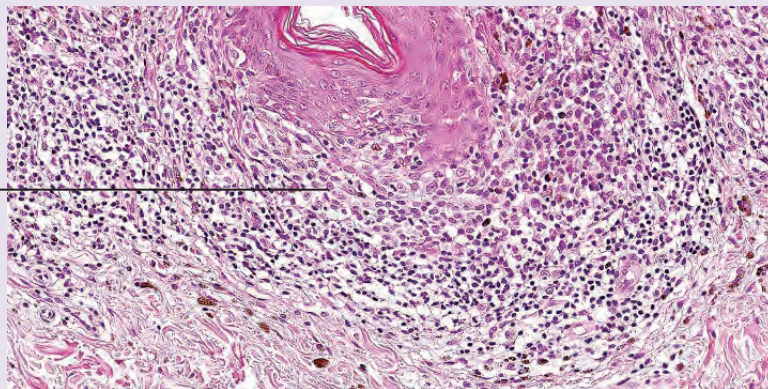
Dome-shaped
lesion with dense
lymphocytic
infiltrate with
melanophages



COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Halo Nevus (Leukoderma Centrifugum Acquisitum; Sutton Nevus)

Remnants of
junctional nevus



Cl: Solitary or multiple, mostly in children and young adults. Depigmented outer ring around a nevus or remnants of an involuted nevus in the center. Late lesions of Sutton nevus quite often are repigmented and the diagnosis can only be established histologically.

Hi:

- Remnants of irregularly shaped junctional, compound or dermal nevus cell nests
- Diminished/absent melanocytes at the periphery of the lesion
- Dense infiltrate composed of lymphocytes, camouflaging the pre-existing melanocytic nests
- Inflammatory cells throughout the nevus, sometimes with signs of incipient regression at the shoulders
- Focal epithelial atrophy with adjacent bands of confluent melanocytes (incomplete consumption of the epidermis)
- Moderate melanocytic polymorphism without mitoses
- Melanophages are not a leading feature
- Rete ridges preserved. Lesion always slightly dome-shaped, never flat

Immunophenotype: SOX-10, MART-1 or other stains for melanocytes.

DD: Malignant melanoma; Spitz nevus; lichen planus.

References

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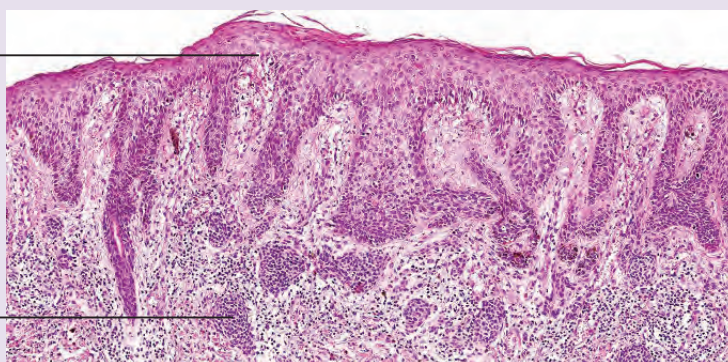
COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Eczematoid Melanocytic (Meyerson's) Nevus

Eczematous reaction on top of a common nevus



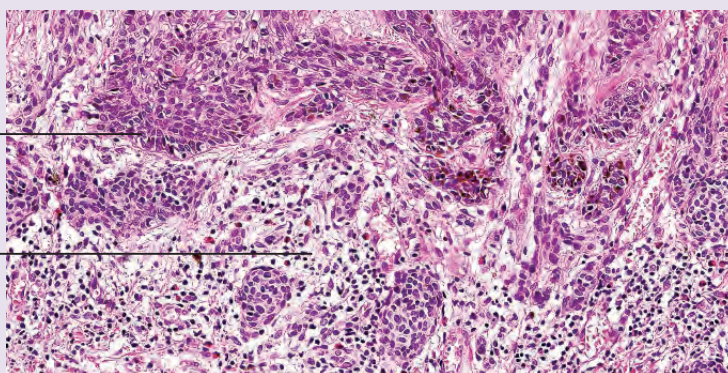
Exocytosis and spongiosis



Nests of melanocytes

Multiple single melanocytes in the basal layer

Inflammatory lymphohistiocytic infiltrate with eosinophils



Cl: Common nevus with eczematous oozing and crusty surface. No history of injury.

Hi:

- Acanthosis and spongiosis of the epidermis reflecting eczematous changes that are restricted to the site of the melanocytic proliferation, stopping at the shoulders
- Common junctional, compound or congenital nevus in the upper dermis
- Junctional and early lesions with a multitude of isomorphic single melanocytes, some of them above the basal layer
- Homogeneous proliferation pattern
- Lymphohistiocytic infiltrate with eosinophils in the upper dermis between nests of melanocytes

COMMON ACQUIRED MELANOCYTIC NEVI

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Variant: Osteo-Nevus of Nanta



Metaplastic bone formation in a common dermal nevus

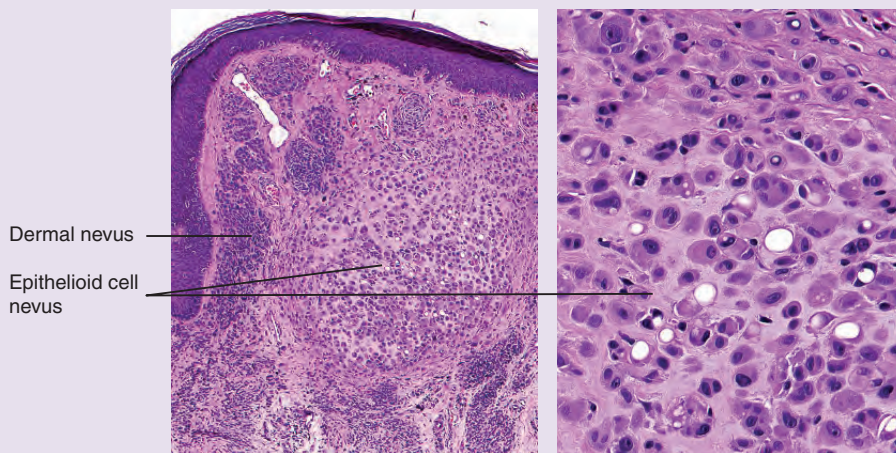
Cl: Common nevus.

Hi: Osteoma cutis in association with a common dermal nevus; metaplastic ossification within or at the base of the lesion.

References

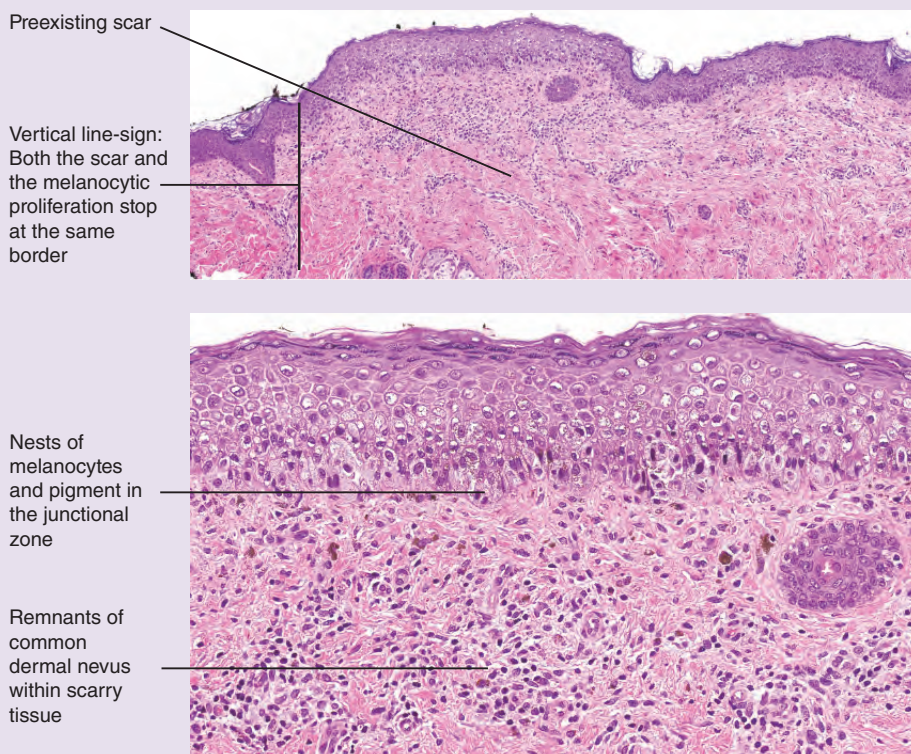
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COMMON ACQUIRED MELANOCYTIC NEVI

**Variant: Combined Epithelioid Spitzoid Nevus, "Wiesner Nevus"
(BAP-1 Deficient Epithelioid Melanocytic Tumor)**

Hi: Features of a common junctional or dermal nevus combined with a banal or cellular blue

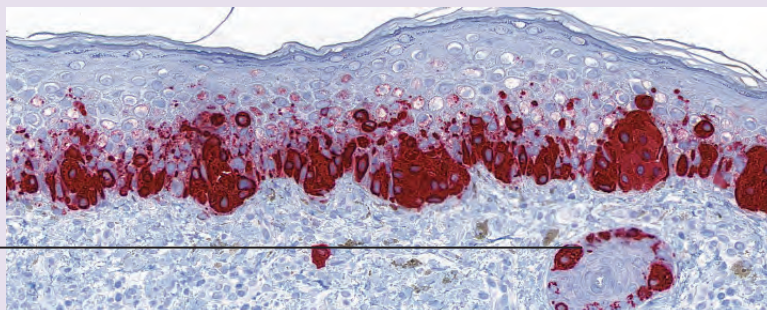
nevus. Both nevus variants may lie side by side, or gradually blend into each other.

Variant: Recurrent (Persistent) Melanocytic Nevus (Pseudomelanoma)

COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Recurrent (Persistent) Melanocytic Nevus (Pseudomelanoma)

Melanoma-pattern:
S100-positive
melanocytes at
the junction and
within the hair
follicle



CI: Scar, usually showing irregular pigmentation, following incomplete surgical removal (shave) or injury with accidental partial removal of a former common melanocytic nevus.

Hi:

- Well-circumscribed melanocytic proliferation, strictly overlying a pre-existing scar
- No lateral spread: junctional melanocytic nests stop at either end of the scar (“screeching halt” sign)
- Effacement of the epidermal rete ridges
- Irregular nests of melanocytes in the junctional zone simulating evolving melanoma
- Moderate cytological atypia but no mitoses
- No transepidermal elimination of single melanocytes
- A few scattered melanocytes may be seen above the dermal epidermal junction directly over the scar

- Residual banal dermal nevus nests may be present beneath the overlying dermal scar

DD: Malignant melanoma.

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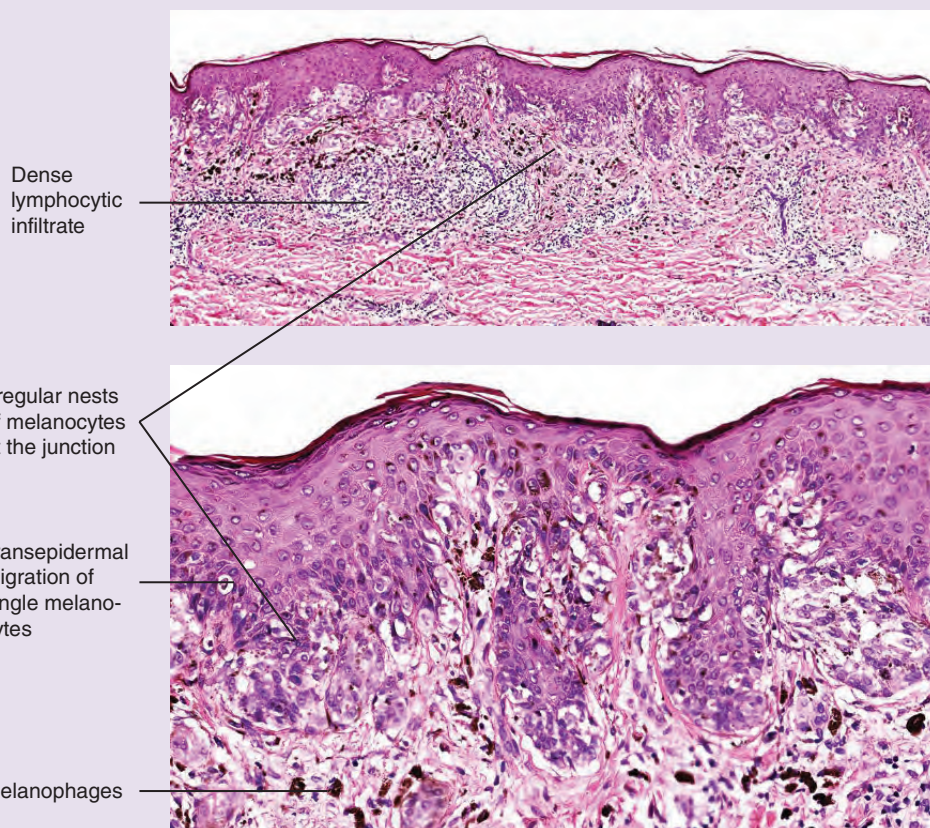
Variant: Nevus in Pregnancy

“Atypical” nevi in
pregnancy



COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Nevus in Pregnancy



CI: Atypical changes can be seen in some melanocytic nevi during pregnancy.

Hi:

- The lesion is symmetrical and sharply demarcated, showing features of an activated nevus
- Junctional “activity” with irregular melanocytic nests
- Few single melanocytes above the basal layer, but no pagetoid melanocytic pattern
- Low mitotic activity may be present
- Melanophages and inflammatory infiltrate in the dermis

DD: Malignant melanoma; melanoma arising in a pre-existing nevus.

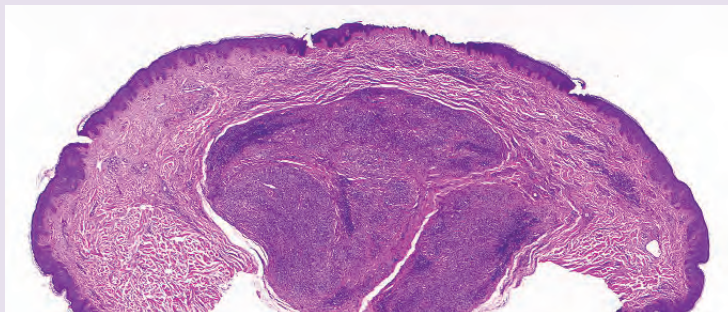
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COMMON ACQUIRED MELANOCYTIC NEVI

Variant: Ancient Nevus

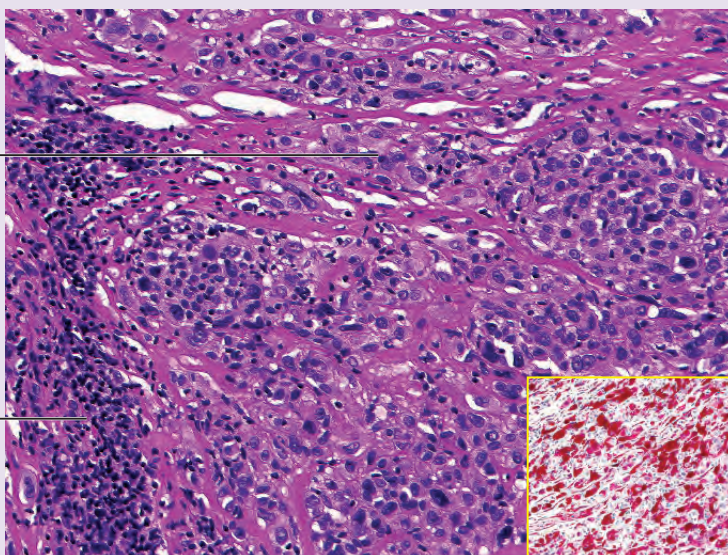
Dermal “ancient” nevus, showing zonation pattern



Inner zone with highly atypical melanocytes

Outer zone of small polymorphic melanocytes

Inset: p16 positive cells



CI: Simulator of malignant melanoma. Head and neck area of adults. Papular or nodular lesion resembling common dermal (Miescher) nevus. Named in analogy to ancient schwannoma.

Hi:

- Pleomorphic dermal nevus with prominent zonation pattern
- Outer zone composed of small- to medium-sized, slightly polymorphic melanocytes with moderate accompanying inflammatory infiltrate
- Inner zone composed of confluent nests and sheets with highly atypical and pleomorphic melanocytes, some of them with spitzoid and rhabdoid features
- Very few mitoses (<2 per section)

Immunohistochemistry: Loss of nuclear BAP-1 expression in conjunction with cytoplasmic VE1 positivity (*BRAF* V600E mutation).

DD: Malignant melanoma; melanoma metastasis; atypical spitzoid tumor.

Comment: Recently, ancient nevus has been subsumed under the heading of BAP1-deficient melanocytic proliferations (“BAP-oma”) which may occur sporadically as well as in the context of a germline mutation with accompanying familial cancer syndrome. Gradual transition from ancient nevus to malignant melanoma in a multistep process is possible.

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BLUE NEVI

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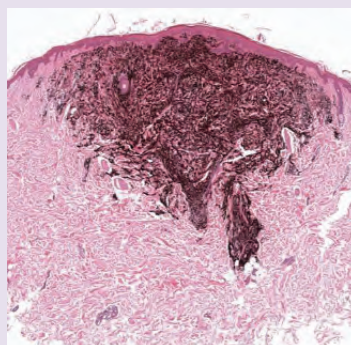
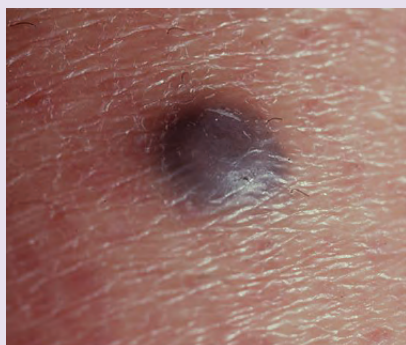
Wiesner, T., Obenaus, A.C., Murali, R., et al. (2011) Germline mutations in BAP1 predispose to melanocytic tumors. *Nat Genet* **43**(10): 1018–21.

Blue Nevus

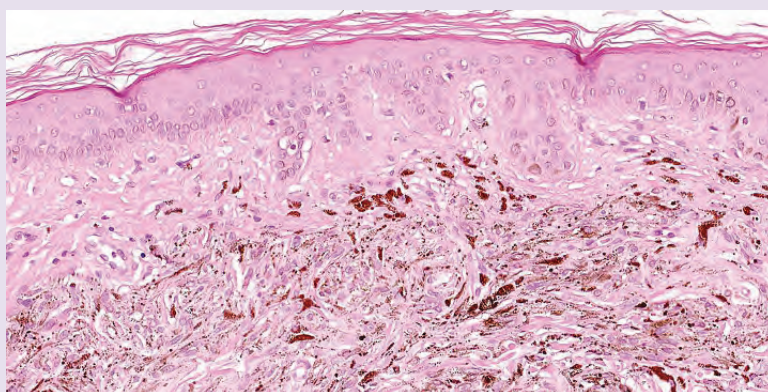
Several morphological variants exist, depending on the degree of stroma fibrosclerosis and melanocytic cellularity.

Common Blue Nevus

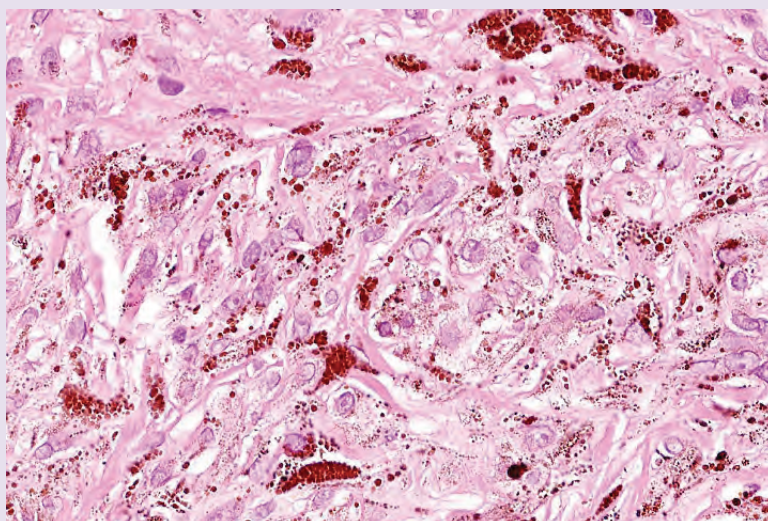
Sharply demarcated hyperpigmented melanocytic lesion in the dermis



Pigmented, dendritic and stellate melanocytes together with melanophages



Accumulation of melanin dispersed within melanocytes and within melanophages



VARIANTS OF COMMON BLUE NEVUS

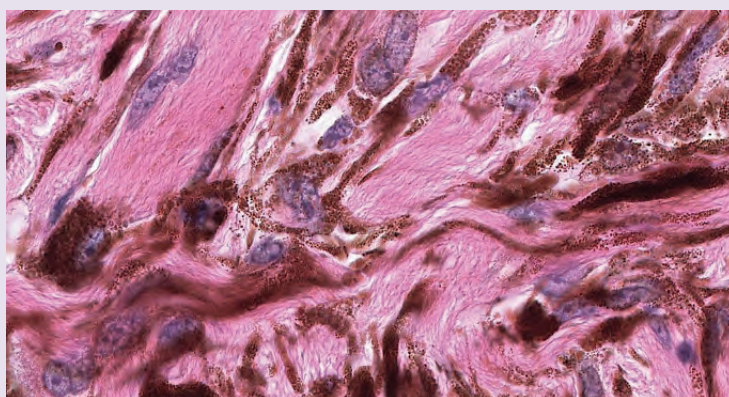
Cl: The typical lesion is a well-circumscribed dome-shaped bluish-black papule. The color is due to the localisation of dispersed pigment in mid and deep dermis.

Hi:

- Normal epidermis
- No junctional melanocytic nests
- Single or fascicularly arranged elongated, bipolar or stellate dendritic melanocytes between densely packed dermal collagen
- Dense accumulation of fine melanin dispersed within the melanocytes and within melanophages
- Melanocytes sometimes aggregating around appendages and neurovascular tissue
- Variable degree of fibrosis; sclerotic stroma in most cases

Common Blue Nevus

Pigmented bipolar, dendritic and stellate melanocytes



- Superficial variant is limited to the upper half of the dermis
 - Remarkably, junctional activity is always completely missing, with the exception of deep penetrating nevus
 - Deep penetrating nevus affects the whole thickness of the dermis, including the dermal-epidermal junction, and may reach into the subcutaneous fat
 - Combined nevus (see above): collision of two types of nevus, mostly banal congenital nevus and common blue cellular nevus
 - Pigmented epithelioid melanocytoma and Carney's syndrome-associated blue nevus: large atypical spitzoid melanocytes may be present, albeit without mitoses
 - Presence of any necrosis may suggest malignant transformation
 - Cellular blue nevus (neuro-nevus) showing deep-reaching, dumb bell-shaped pale cellular fascicles of melanocytes with overlying common blue nevus in the upper dermis (see below)
- DD:** Malignant blue nevus is a morphological variant of heavily pigmented malignant melanoma; blue nevus-like metastasis of malignant melanoma: patches of atypical hyperpigmented melanocytes in a blue nevus-like pattern, often accompanied by inflammatory infiltrate and mitoses; dermal melanocytosis, indistinguishable from nevus Ota or nevus Ito; nodular melanoma; hydrocystome noire; hemosiderotic dermatofibroma.

References

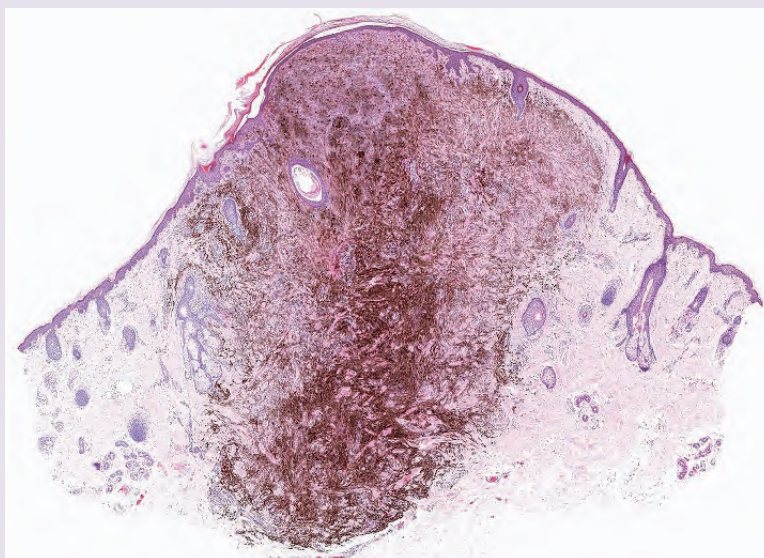
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VARIANTS OF COMMON BLUE NEVUS

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Variant: Deep Penetrating Blue Nevus

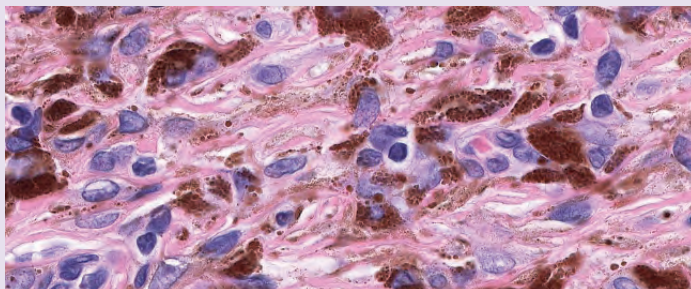
Melanocytes and pigment throughout the dermis reaching into the subcutis



VARIANTS OF COMMON BLUE NEVUS

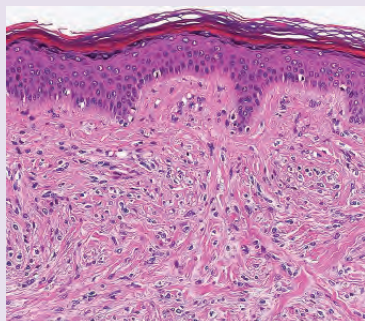
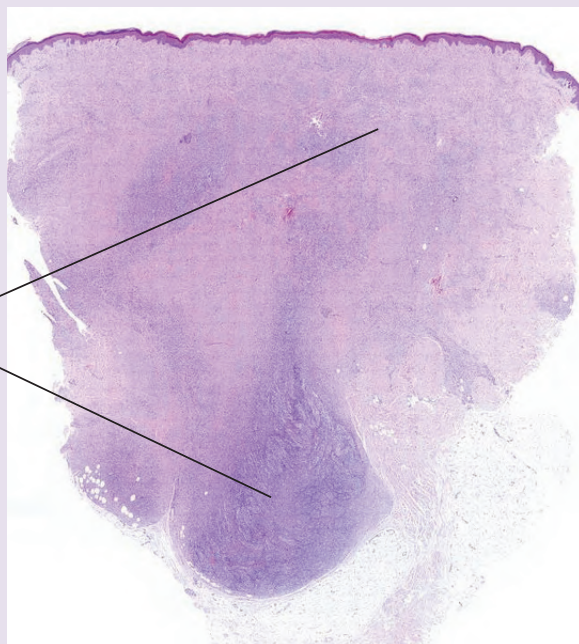
Variant: Deep Penetrating Blue Nevus

Enlarged melanocytes with vesicular nuclei. Some epithelioid hyperpigmented melanocytes

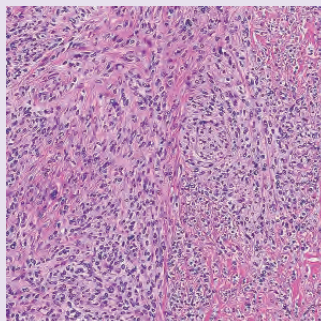


Variant: Cellular Deep Penetrating Blue Nevus (Neuro-Nevus)

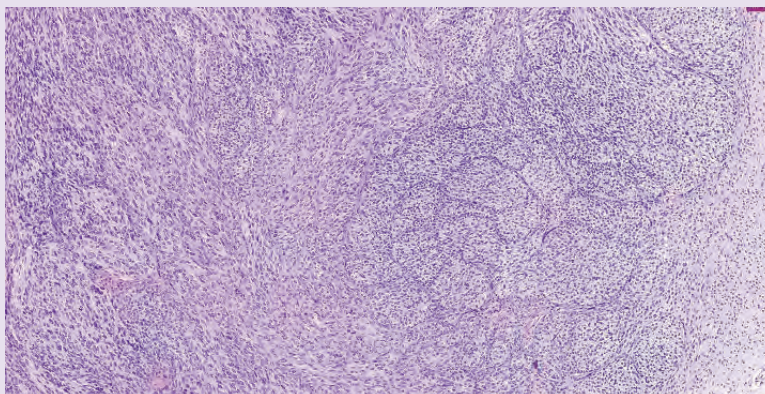
Pattern of banal blue nevus on top, "dumb-bell pattern" of cellular nevus at the bottom



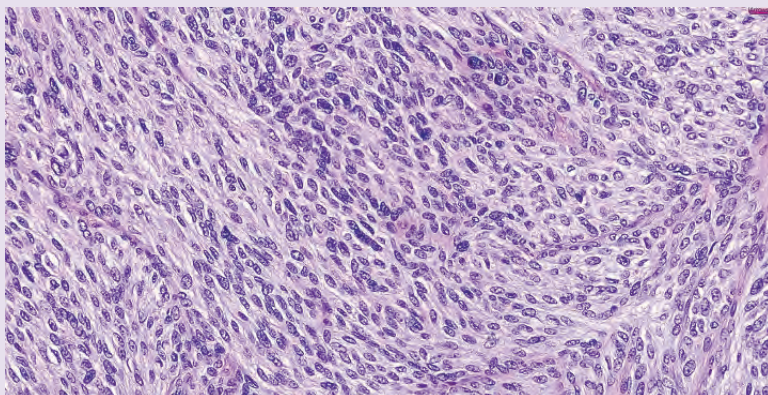
Subepidermal part



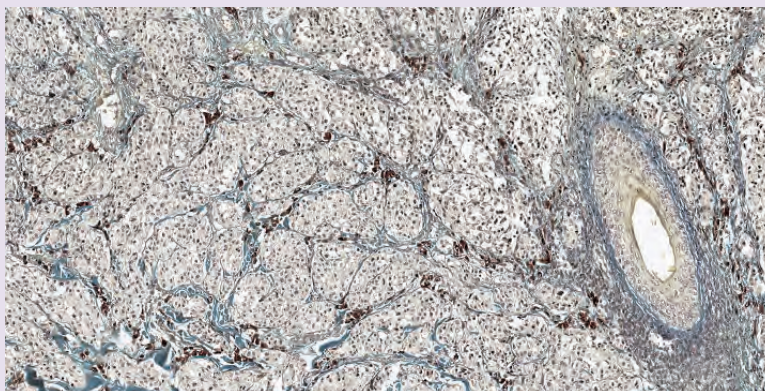
Deep dermal part

VARIANTS OF COMMON BLUE NEVUS**Variant: Cellular Blue Nevus, Hypopigmented**

Nests and
bundles of
densely packed
melanocytes



Elastica stain

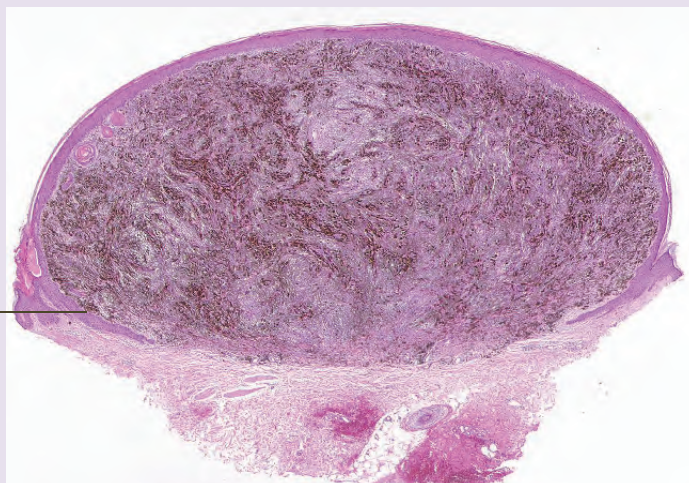


VARIANTS OF COMMON BLUE NEVUS

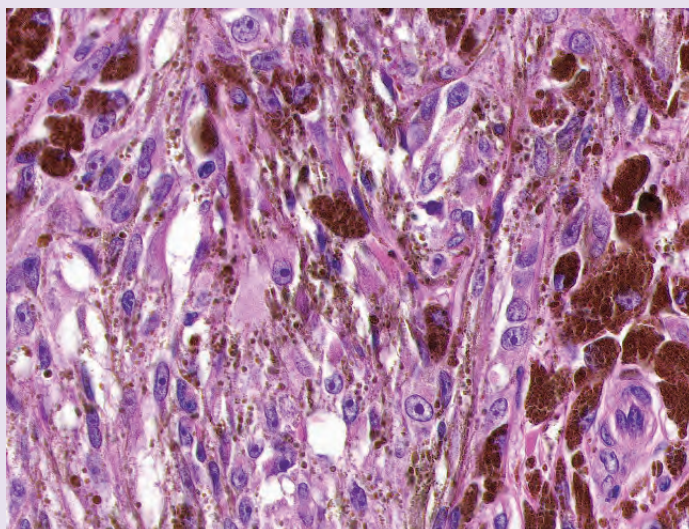
Variant: Pigmented “Epithelioid” Blue Nevus

Well circumscribed
pigmented nodule
in the dermis

Pincer-like rete
ridges at the
border



Large “epithelioid”
pigment loaded
melanocytes



Cl: Features of common dermal nevus.

Hi:

- Symmetrical wedge-shaped or multi-wedge-shaped (“inverted pyramids”) deep penetrating melanocytic proliferation, involving the entire dermis
- Pattern of banal blue nevus on top, dumb bell pattern of cellular nevus at the bottom
- Throughout the entire lesion, small nests composed of pigmented banal melanocytes and larger (“spitzoid”) melanocytes with ample cytoplasm and vesicular nuclei showing various degrees of pigmentation

- Large melanophages, evenly distributed in a “net-like” pattern throughout the lesion
- No significant pleomorphism
- Very few mitoses (<2 per lesion)
- Multistep evolution into melanoma has been reported, with multiple mitoses as a significant indicator of transformation

DD: Malignant melanoma; pigmented epithelioid melanocytoma (PEM); Carney syndrome-associated nevus.

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DERMAL MELANOCYTOSIS

Proliferative nodule in melanocytic nevi mimicking deep penetrating nevus. *An Bras Dermatol* **92**(2): 231–3.

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Dermal Melanocytosis

Nevus Fuscoceruleus (Ota; Ito; Mongolian Spot)

Nevus fusco-
coeruleus
trigeminus II (left)

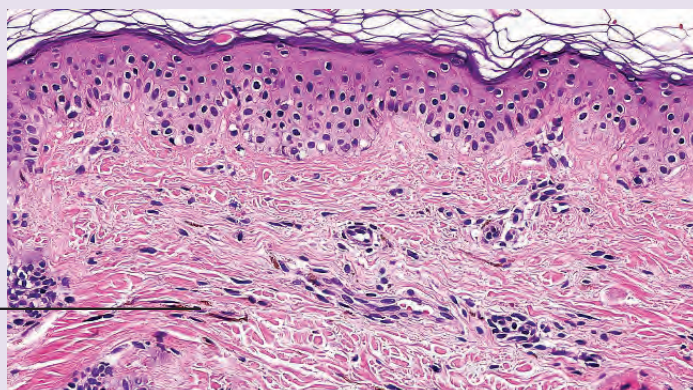
Naevus fusco-
coeruleus
trigeminus I (Ota)
(right)



Mongolian spot



Pigmented
dendritic
melanocytes



SPINDLE AND/OR EPITHELIOID CELL NEVUS

Dermal melanocytoses are macular variants of blue nevi in special localisations. Lesions are present from birth or appear in childhood.

Cl:

- Nevus Ota (nevus fuscoeruleus ophthalmomaxillaris) involving neural innervation domains of branch I or II of the trigeminal nerve (V. cranial nerve)
- Nevus Ito (acromiodeltoideus) involving the shoulder girdle

- Mongolian spot involving the sacral area

Hi: Remarkably, only a few dendritic melanocytes and scarce scattered pigment are found throughout the upper and mid dermis (“invisible dermatosis”).

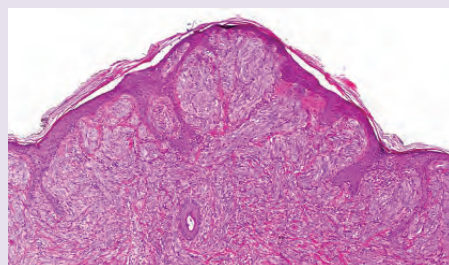
Immunohistochemistry: Melan A or S100 stains allow unequivocal diagnosis.

Spindle and/or Epithelioid Cell Nevus

Common Nevus of Spitz

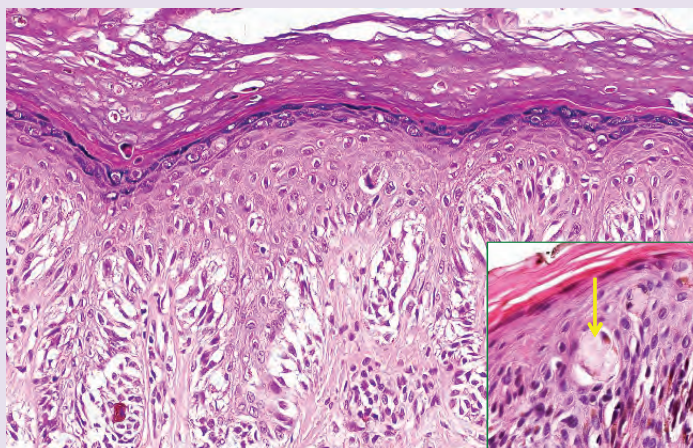
Typical Spitz nevus on the cheek of a child

Dome-shaped lesion with elongation of rete ridges (right)

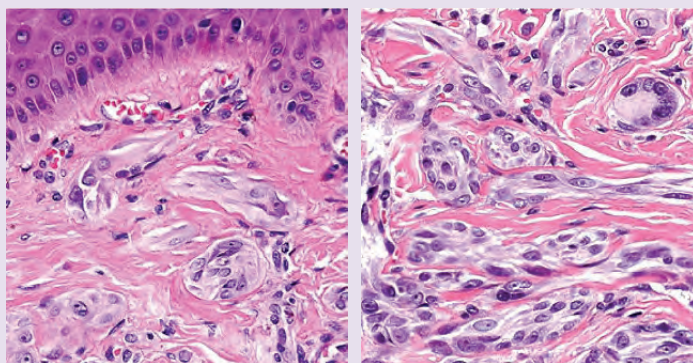


Fascicles of melanocytic spindle cells in the junctional zone

Inset: Suprabasal Kamino body (arrow)



Spindle (left) and multinucleate cells (right) in the upper dermis



SPINDLE AND/OR EPITHELIOID CELL NEVUS

Cl: Pink or red-brown well-circumscribed papule with smooth surface, preferentially developing over several months in the face of children and young adults. Multiple, grouped or agminated lesions can occur.

Hi:

- Exophytic growth pattern
- The shape of the lesion is symmetrical, the bottom is usually flat or pyramid-like wedge shaped, lateral borders are sharp
- The hallmarks are nests of uniform large spindle-shaped and epithelioid melanocytes in the papillary dermis and between elongated rete ridges
 - Epithelioid cells with amphophilic eosinophilic cytoplasm, centrally located nucleus and relatively large nucleolus; fine dispersed chromatin
 - Fusiform spindle cells arranged as fascicles in vertical orientation
- Abundant “ground glass” cytoplasm of spindle cells and epithelioid cells
- Multinucleated cells may be present
- Clefts between the nests and the adjacent keratinocytes
- Eosinophilic amorphous pink globules of degenerative basement membrane material (Kamino bodies) in the lower part of the epidermis

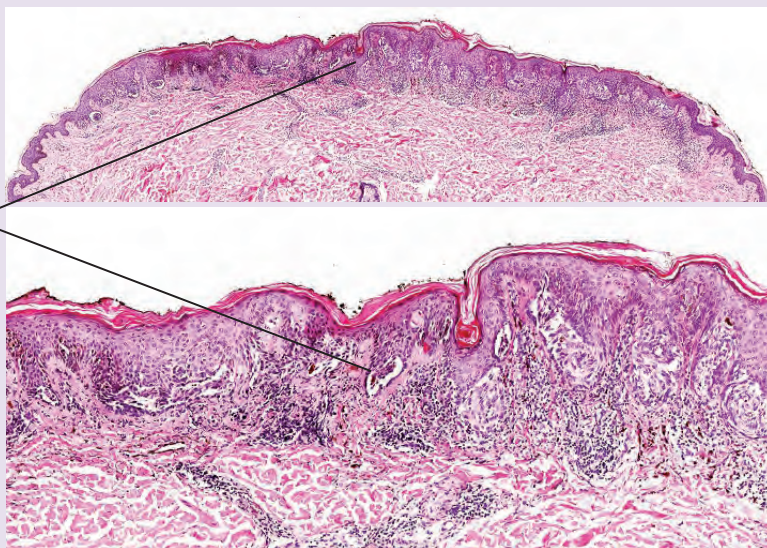
- “Maturation” of the melanocytes from the top of the lesion with larger nests at the dermoepidermal junction to smaller nests and single cells in the deeper parts of the nevus
- Few mitoses in the upper dermal parts – minimal mitotic activity at the base
- Sometimes lymphocytic infiltrate
- Asymmetry, lack of maturation, and multiple mitoses at the base are criteria of severe atypia and presumed malignant transformation (AST: atypical spitzoid tumor)
- Comparative genomic hybridization can be helpful in separating benign lesions and spitzoid melanoma
- Frequent HRAS gene mutation

Variants of Spindle and Epithelioid Cell Nevus

- Junctional type
- Compound type
- Dermal type
- Desmoplastic forms with sclerotic stroma and interspersed single spitzoid melanocytes
- Balloon cell variant
- Pagetoid variant
- Intraoral nevus

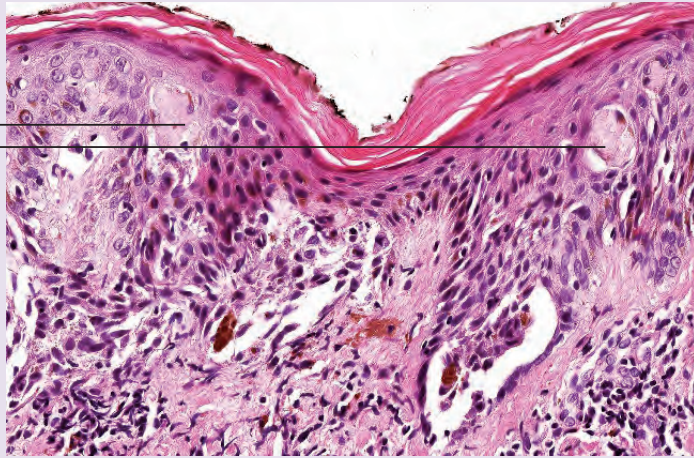
Variant: Nevus Spitz, Junctional

Nests of spindled and epithelioid cells at the junction. Clefts around most nests.

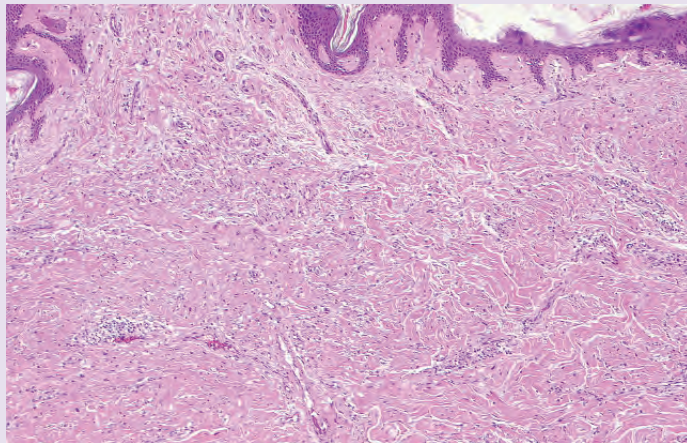


Variant: Nevus Spitz, Junctional

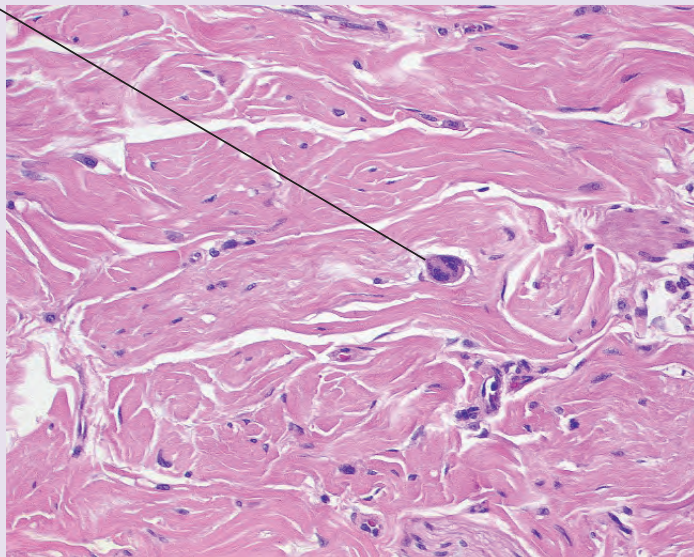
Kamino
bodies



Variant: Atypical (Desmoplastic or Sclerosing Nevus Spitz)



Large atypical melanocytes, solitary or grouped, in a background of thick collagen bundles



SPINDLE AND/OR EPITHELIOID CELL NEVUS

DD: Spitzoid melanoma; common melanocytic nevus; mastocytoma; juvenile xanthogranuloma; fibrohistiocytic proliferations (S100 negative).

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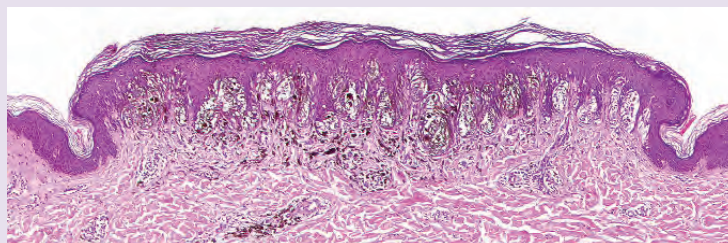
SPINDLE AND/OR EPITHELIOID CELL NEVUS

Variant: Pigmented Spindle Cell Nevus (Reed)

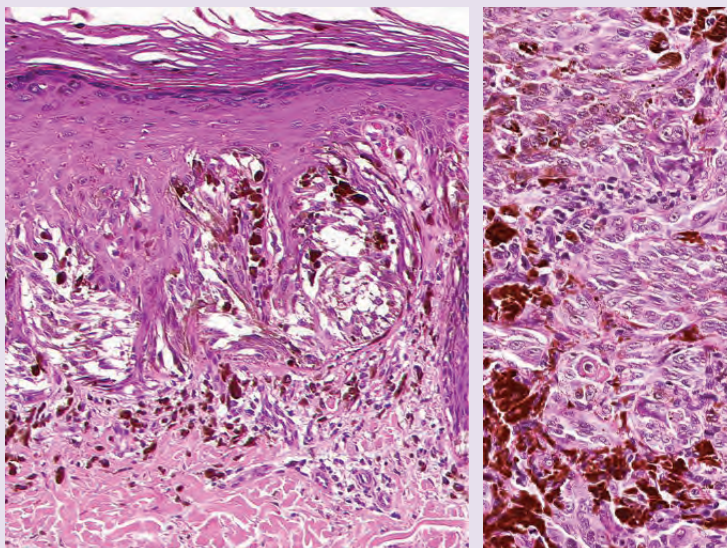
Dark homogeneously pigmented lesions on the cheek (left) and on the arm (right)



Junctional and intraepidermal pigmented nests of melanocytes



Spindle cells (left) and epithelioid cells (right) with pigment



The pigmented spindle cell nevus of Reed is considered a nevus entity of its own, always presenting as a heavily pigmented (black) circumscribed symmetrical nevus.

Cl: Heavily pigmented (jet black) symmetrical, sharply circumscribed macule or flat papule, preferentially on the trunk or extremities of adults.

Hi:

- Strikingly symmetrical and sharply circumscribed superficial melanocytic lesion
- Junctional or compound lesion with nests of heavily pigmented slender and spindled melanocytes

BENIGN MELANOCYTIC LESIONS WITH PECULIAR STRUCTURAL FEATURES

- Broad, horizontally arranged band of heavily pigmented melanophages underlying the lesion
- Fascicles of spindle cells in nest-like arrangement, mostly at the junction
- Evolving (intraepidermal) lesions with irregularly spaced spindles and slightly epithelioid melanocytes in the lower parts of the epidermis
- No mitoses
- Often overlying band of compact orthokeratosis with deposits of melanin granules

DD: Common pigmented nevus; malignant melanoma.

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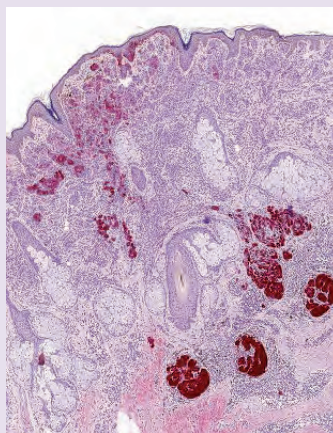
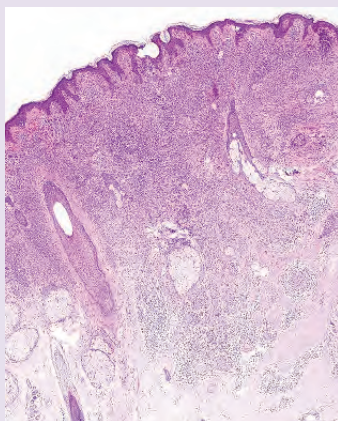
Yoradjan, A., Enokihara, M.M., and Paschoal, F.M. (2012) Spitz nevus and Reed nevus. *An Bras Dermatol* **87**(3): 349–57; quiz 358–9.

Benign Melanocytic Lesions with Peculiar Structural Features

Benign clonal expansions in melanocytic nevi are considered to be expressions of different *NRAS* mutations in conventional nevi.

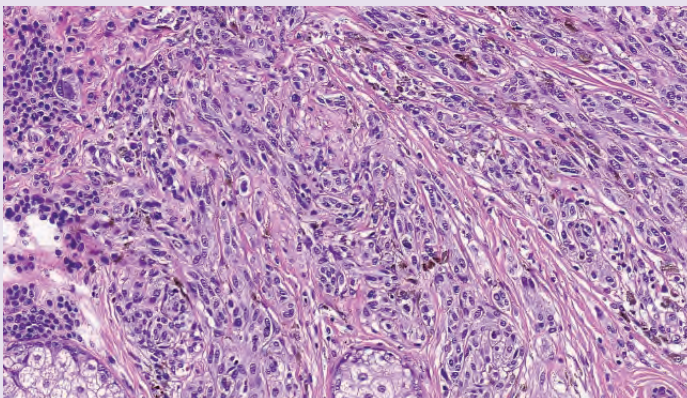
Melanocytic Nevus with Clonal Proliferation

Dermal nevus (left) showing clones of HMB45-positive melanocytes (right)



HMB45

Clones of variably shaped melanocytes

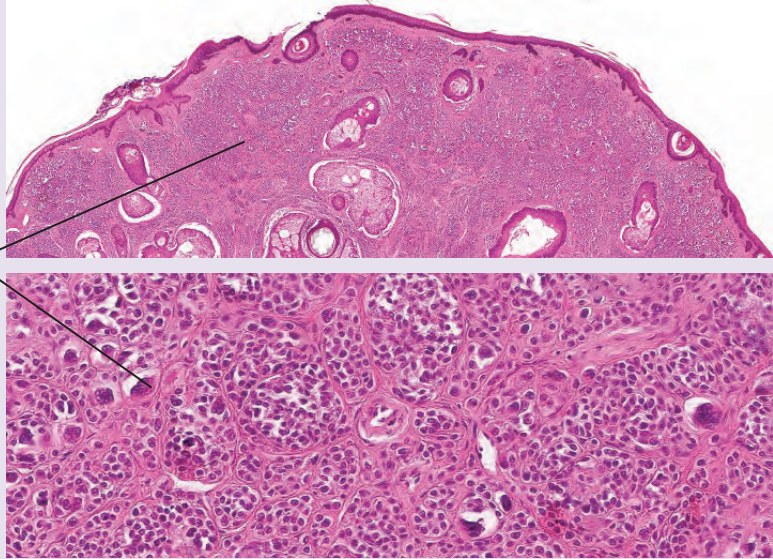


BENIGN MELANOCYTIC LESIONS WITH PECULIAR STRUCTURAL FEATURES

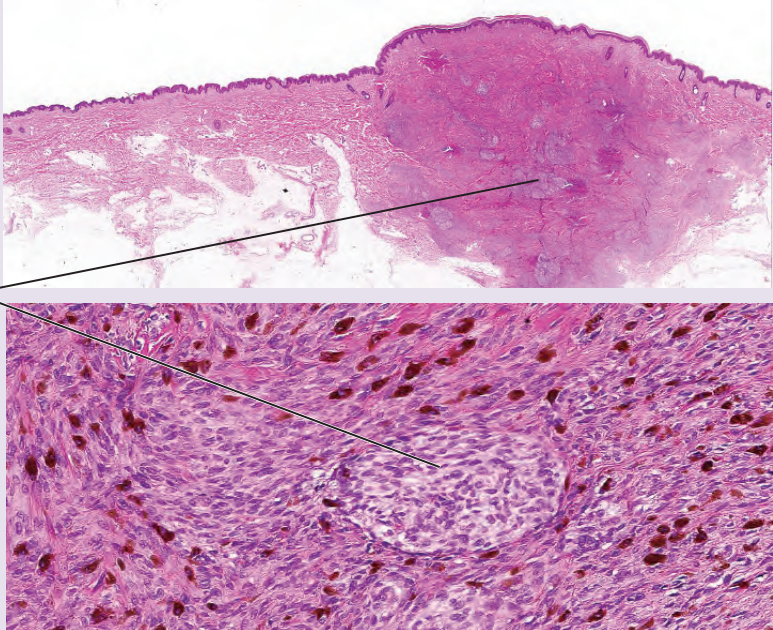
CI: Common melanocytic nevi.

Clonal Proliferation in Congenital Nevus

Nests of melanocytes containing multinucleated cells



Nests of spindle shaped melanocytes



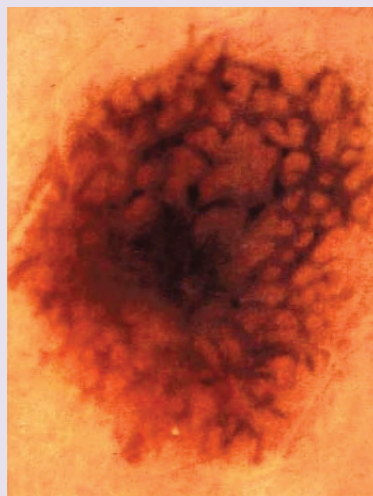
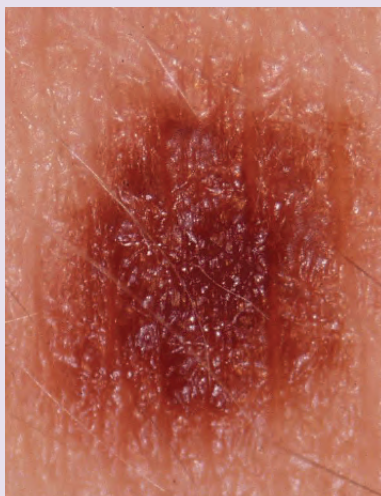
Hi: Within banal congenital dermal nevus there are circumscribed single or multiple nests of larger, roundish melanocytes and melanophages, without mitotic activity.

Immunohistochemistry: Distinct HMB45 expression.

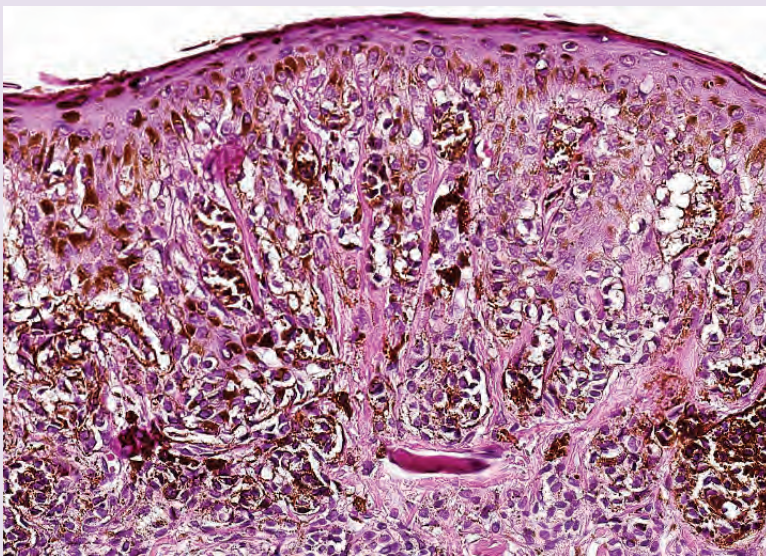
BENIGN MELANOCYTIC LESIONS WITH PECULIAR STRUCTURAL FEATURES

Atypical (Dysplastic) Melanocytic (Clark's) Nevus (B-K Mole Syndrome)

Atypical
"dysplastic" nevus
(left). Irregular
net of pigment
seen with the
dermoscope
(right)



Lentiginous
dysplastic nevus:
junctional nevus
with architectural
disorder



When present as multiple lesions in the context of familial genetic predisposition (B-K mole syndrome, described by Clark and by Lynch), the diagnosis is straightforward. However, single lesions are difficult to identify histologically, because (1) the ABCD rule of melanoma may be fulfilled and (2) there is a great variety of melanocytic morphology and it is an issue of endless debates on what is typical, atypical or dysplastic. There is no specific histological feature and no consensus about histopathological definitions of atypia or dysplasia in melanocytic nevi.

The National Institutes of Health Consensus Conference recommended that the term *dysplastic nevus* be abandoned in favor of nevus with architectural disorder or cytologic atypia. Immunosuppression and UV exposure may play an etiological role. Dysplastic nevi may be precursors of melanoma or markers for melanoma susceptibility.

CI: Usually flat or macular, pigmented lesion with ill-defined irregular borders and variable colors within the same lesion, varying from deep to light brown.

BENIGN MELANOCYTIC LESIONS WITH PECULIAR STRUCTURAL FEATURES

Hi: Mostly junctional melanocytic nevus with architectural disorder and cytological atypia.

- Banal dysplastic nevus (Clark's nevus): architecture of a conventional compound nevus with "active shoulders", i.e. small nests and groups of melanocytes tapering out towards the edges of the lesion
- Severely dysplastic nevus: features of a Clark's nevus in conjunction with high cytological atypia, albeit without mitoses and without atypical single melanocytes above the basal layer
- Bridging nests of melanocytes in the junctional zone in conjunction with lamellar fibroplasia
- Cytological features variable: spindle shaped or epithelioid melanocytes possible
- Nuclear pleomorphism (restricted to severely dysplastic nevus): large nuclei with prominent nucleoli

- Minimal mitotic activity (<2 mitoses/section)
- Lymphohistiocytic inflammatory infiltrate with melanophages

DD: Common melanocytic nevus; congenital melanocytic nevus; malignant melanoma.

References

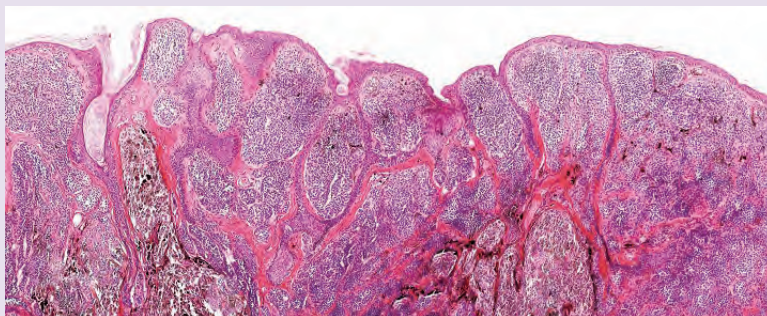
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Congenital Nevi, Small and Medium-Sized (1.5–20 cm)

Small (left) and medium-sized (middle and right) congenital nevi



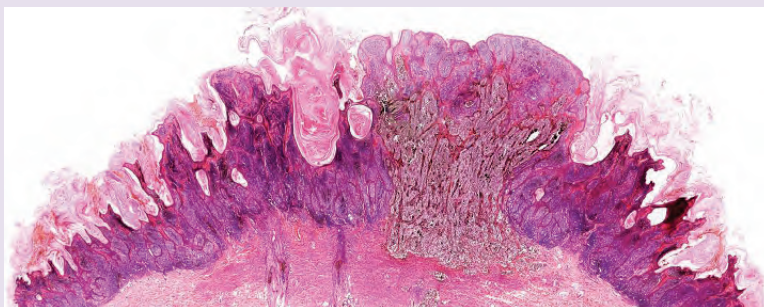
Compound congenital nevus



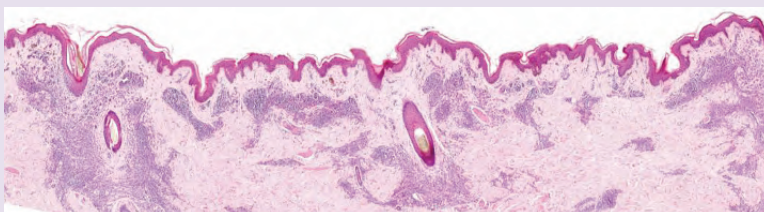
BENIGN MELANOCYTIC LESIONS WITH PECULIAR STRUCTURAL FEATURES

Congenital Nevi, Small and Medium-Sized (1.5–20 cm)

Compound
congenital
nevus with
central clonal
proliferation



Dermal
congenital
nevus



According to an NIH consensus conference (1984), small (0–1.5 cm) to medium-sized (1.5–20 cm) and large (>20 cm) congenital melanocytic nevi are differentiated, the latter showing high risk of CNS involvement and development of melanoma.

Cl: Brown macular lesions with irregular but sharp borders, with or without hairs. Usually lesions are present at birth and get darker over the first months or years of life. Lateral expansion of the nevus congruently with body growth.

Hi: The diagnosis is made clinically. However, histological evaluation of so-called proliferative nodule in congenital nevi is paramount in order to exclude melanoma.

- Features of common junctional (small congenital) and/or compound (large congenital) nevus; involvement of upper and mid dermis
- Nests of melanocytes at the dermal-epidermal junction and in the dermis respectively
- Architectural atypia (especially in young children and adolescents) with irregularly spaced (“dysplastic”) melanocytic nests at the junction and single melanocytes
- Spread of melanocytes along the adnexal structures
- Deep parts may show neuroid differentiation
- Blue nevus-like clonal expansions amidst the nevus nests may be present

Immunohistochemistry: Nuclear H3K27me3 expression within the nodular melanocytes was shown to be a significant indicator of proliferative nodule (benign) versus malignant melanoma.

DD: Congenital nevus in the newborn may present with a melanoma-like scatter of single melanocytes throughout the epidermis, overlying a conventional dermal congenital nevus. Proliferative nodule in a congenital nevus (in a newborn or in an infant) is composed of isomorphic melanocytes that morphologically clearly differ from the adjacent nevus cells. The number of mitoses within the proliferative nodule may be increased. There may be a gradual blending of one melanocytic population into another, as well as a sharp circumscription between proliferative nodule and adjacent nevus.

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LENTIGO MALIGNA DUBREUILH (HUTCHINSON'S FRECKLE)

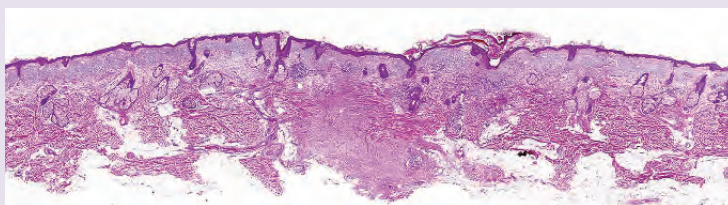
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Malignant Melanocytic Neoplasms**Lentigo Maligna Dubreuilh (Hutchinson's Freckle)**

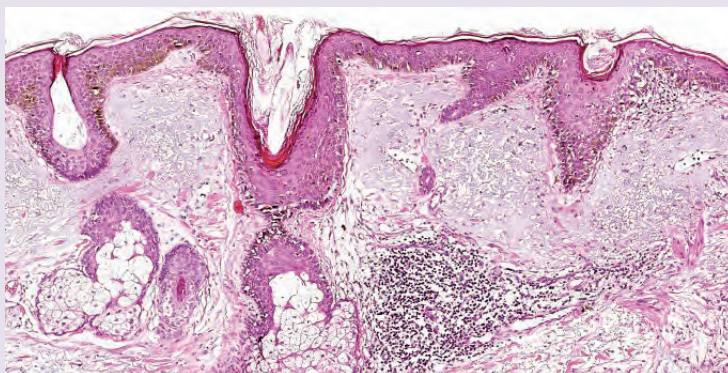
Irregular macular lesions on nose, cheek and neck



Atrophy of the epidermis, massive solar elastosis



Increased number of melanocytes in the basal layer and within the adnexal epithelium



MALIGNANT MELANOMA

Most pathologists consider these lesions not as distinct entities but as melanoma *in situ*. However, there are many reasons to differentiate lentigo maligna from melanoma even though it may turn into lentigo maligna melanoma when not appropriately removed. Immunohistochemical investigation of cell markers (HMB45, S100) does not discriminate between lentigo maligna and melanoma.

Cl:

- Slowly growing (over years and decades) macular lesion in sun-exposed areas of elderly individuals
- Irregular fading borders
- Variable irregular pigmentation
- Slight atrophy
- Good prognosis

Hi:

- Atrophy of the epidermis and flattening of the papillary profile
- Increased number of single atypical large melanocytes in the basal epidermal layer
- No nests of atypical melanocytes in the dermis
- Atypical melanocytes extending down the follicular epithelia to the level of the infundibulum and down eccrine ducts
- Pigment in melanophages in the dermis
- Basement membrane intact; no junctional or basal melanocytic nests
- Horizontal growth
- Solar elastosis in the upper dermis
- There may be scarce lymphocytic infiltrate with scattered plasma cells (typical for the head and neck localisation) in the upper dermis

DD: Flat seborrheic keratosis; recurrent melanocytic nevus; lentigo maligna melanoma; superficial spreading melanoma; pigmented actinic keratosis.

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Malignant Melanoma

Four major variants of malignant melanoma have to be differentiated, clinically and histologically.

- Superficial spreading melanoma (SSM): most common form of melanoma
- Lentigo maligna melanoma (LMM): evolves from lentigo maligna
- Nodular melanoma (NM): red, brown, black tumor, often ulcerating and/or bleeding
- Acral lentiginous melanoma (ALM): nails, fingers, palms, soles

Special clinical variants are melanoma of mucous membrane, conjunctiva, amelanotic melanoma, genital melanoma.

The ABCD rule (A – asymmetry, B – border, C – colour, D – diameter) serves the clinician in discriminating malignant melanoma from benign melanocytic or other simulators.

Comment: It has become the standard of care that for virtually all melanomas, testing for BRAF mutations and GNAQ/KRAS should be performed, indicating various morphological subtypes.

Reference

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MALIGNANT MELANOMA

Variant: Superficial Spreading Melanoma (SSM)

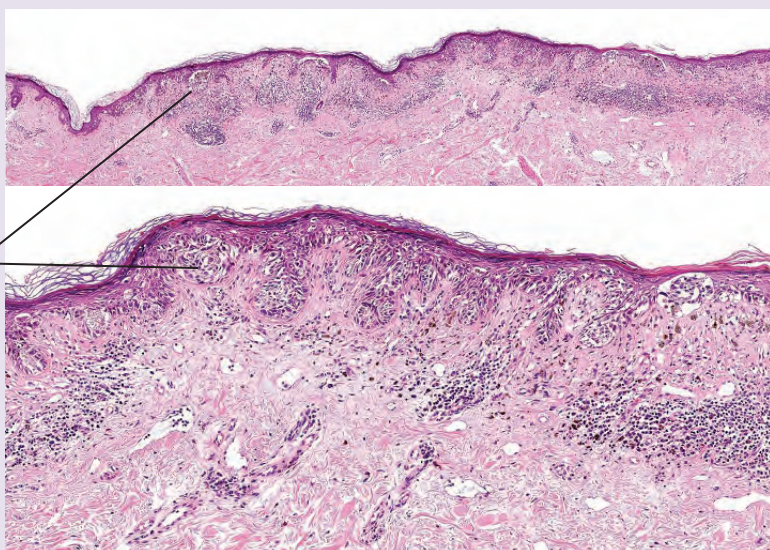
Superficial spreading melanoma with amelanotic tumor nodule in the center (left)



Superficial spreading melanoma with tumor regression in the center (right)

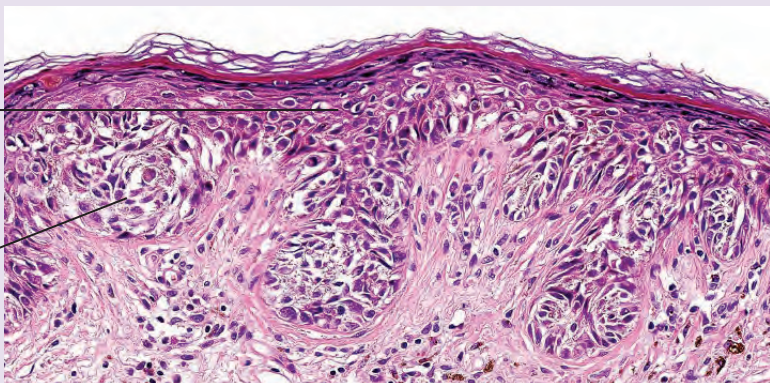


SSM, nests of tumor cells at the junction and in the upper dermis



Transepidermal elimination of single melanocytes

Nests of atypical melanocytes



MALIGNANT MELANOMA

Cl: Preferentially on the legs of women but also at any other localisation. Round or oval, horizontally growing pigmented flat lesion with irregular sharp polycyclic borders. Tendency for central regression and sometimes resulting in an incomplete ring structure. Depigmentation in the middle of the lesion does not necessarily mean complete resolving of tumor cells in this area of immunological reaction. Over time, vertical growth can start. A variable spectrum of colors may be seen from white (regression zones) to red (inflammation), brown, and black.

Hi:

- Slightly acanthotic epidermis
- Spread of atypical melanocytes as single cells or in small clusters throughout all levels of the epidermis, featuring a pagetoid pattern
- Large tumor cells with abundant cytoplasm
- Nuclei are irregular, chromatin is clumped, nucleoli are prominent
- Balloon cell variants exist
- Some mitotic activity is usually present
- Involvement of adnexal epithelium
- Epidermal basement membrane effaced by proliferation of atypical melanocytes
- Infiltration of papillary dermis
- Irregular distribution of melanin preferentially on the bottom of the lesion and in dermal melanophages
- Fibrosis in the papillary dermis in areas of regression
- Scattered inflammatory infiltrate
- Vertical growth can arise after variable time of horizontal growth
 - Starting from one or several areas of the superficially spreading tumor
 - Invasion of mid and deeper parts of the dermis
 - May be associated with increased cellular atypia

DD: Solar lentigo; pigmented basal cell carcinoma; Bowen's disease; pigmented Paget's disease of the breast.

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Hasbun Acuna, P., Cullen Aravena, R., Maturana Donaire, C., Ares Mora, R., and Porras Kusmanic, N. (2016) Pigmented basal cell carcinoma mimicking a superficial spreading melanoma. *Medwave* **16**(11): e6805.

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Hikawa, R.S., Kanehisa, E.S., Enokihara, M.M., Enokihara, M.Y., and Hirata, S.H. (2014) Polypoid melanoma and superficial spreading melanoma different subtypes in the same lesion. *An Bras Dermatol* **89**(4): 666–8.

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Scope, A., Zalaudek, I., Ferrara, G., Argenziano, G., Braun, R.P., and Marghoob, A.A. (2008) Remodeling of the dermoepidermal junction in superficial spreading melanoma: insights gained from correlation of dermoscopy, reflectance confocal microscopy, and histopathologic analysis. *Arch Dermatol* **144**(12): 1644–9.

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MALIGNANT MELANOMA

Variant: Lentigo Maligna Melanoma (LMM)

Invasive melanoma arising in long standing lentigo maligna

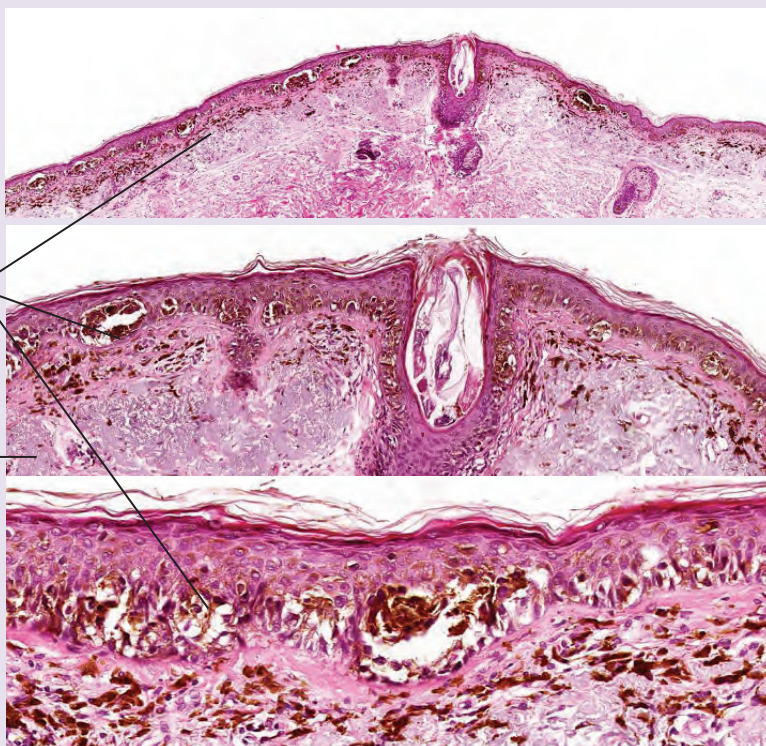
Moulage of lentigo maligna melanoma (courtesy of the Moulage Museum of the University and the University Hospital of Zürich; Dr. M Geiges)



Atrophy of the epidermis

Nests of atypical melanocytes at the dermo-epidermal junction and within the papillary dermis

Solar elastosis



Cl: Remnants of macules of lentigo maligna. After some years flat plaques or nodules arise due to the spread of tumor cells with invasive growth into the dermis.

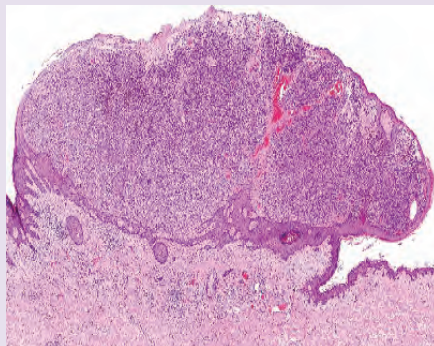
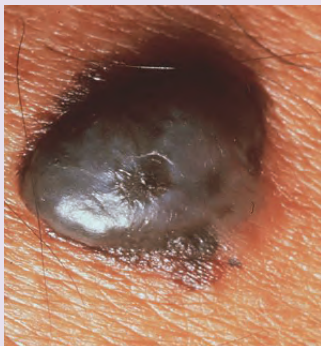
Hi: Like lentigo maligna, but with invasion of malignant melanocytes beyond the epidermal

basement membrane into the papillary dermis. Predominantly spindle-shaped dermal melanocytes in many cases, merging with desmoplastic melanomas.

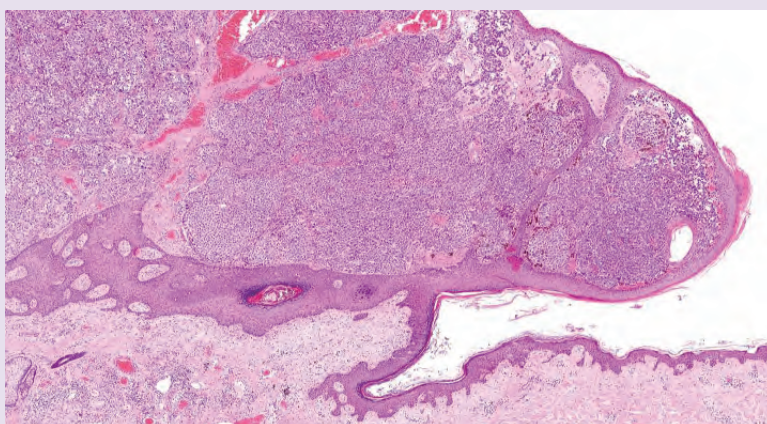
MALIGNANT MELANOMA

Variant: Nodular Melanoma (NM)

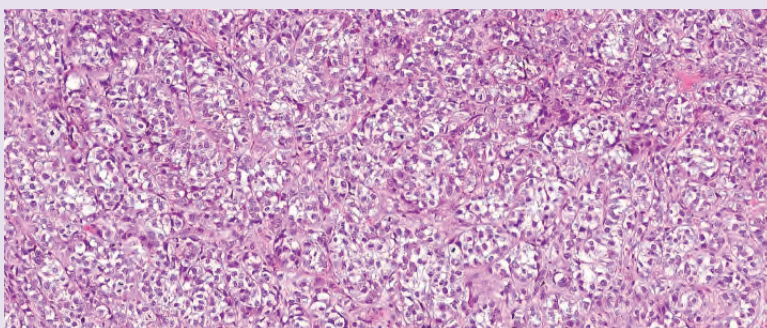
Darkly pigmented nodular melanoma (left)



Lateral aspect of exophytic and invasive growing nodular paucimelanotic melanoma (upper right and mid)



Large atypical hypopigmented melanocytes with prominent nuclei



Cl: Dark, rapidly growing nodule, usually arising on normal skin. Loss of skin tension lines and pilosebaceous follicles. The surface is smooth or ulcerated and crusty. The surrounding skin may show hyperpigmentation and small local satellites.

Hi:

- Exophytic tumor
- Large atypical melanocytes
- Variable cytomorphology, including spindle-shaped, epithelioid, clear cells and others

- Minimal epidermal but deep dermal invasion
- High mitotic activity

DD: Melanoma metastasis.

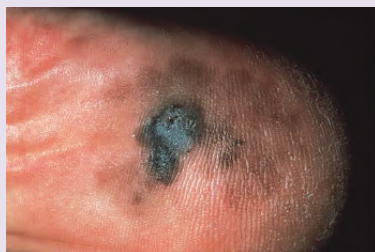
Reference

Gescheidt-Shoshany, H., Weltfriend, S., and Bergman, R. (2015) Nodular melanoma arising in a large segmental speckled lentiginous nevus. *Am J Dermatopathol* 37(8): 663–4.

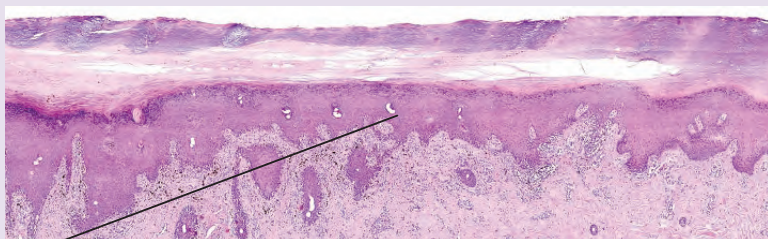
MALIGNANT MELANOMA

Variant: Acral Lentiginous Melanoma (ALM)

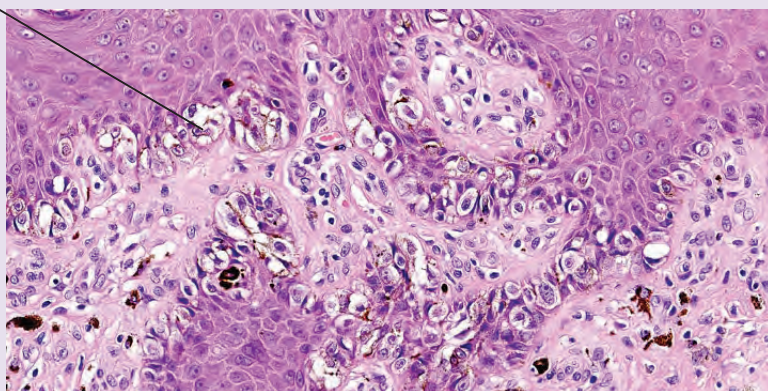
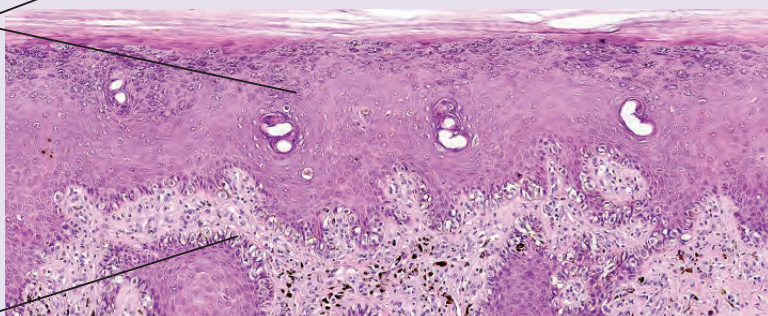
ALM on the heel (left) and on the planta and toes (right)



Hyperkeratosis and acanthosis of plantar epidermis



Closely spaced atypical melanocytes along the basal layer



Cl: Slowly growing, pigmented macule in acral localisation such as toes or fingers, starting from the nail matrix, nailbed or nailfold or on palms and soles, preferentially in black people. Loss of regular dermatoglyphs may give a diagnostic hint. Similar lesions can occur on mucous membranes.

Hi: Similar to lentigo maligna melanoma.

- Large, atypical melanocytes, initially distributed as single cells or in small clusters throughout the basal layer of the epidermis, later throughout the entire epidermis (pagetoid spread)

MALIGNANT MELANOMA

- Transepidermal elimination of pigment and single cells
- Fibrosis and scattered lymphocytic infiltrate in the upper dermis
- Migration of atypical cells into the papillary dermis
- The tumor spreads laterally
- Involvement of adnexal epithelium
- Frequent KIT gene mutation

DD: Intracorneal bleeding (“black heel”); superficial spreading melanoma; acral melanocytic nevus.

References

- Donati, P., Paolino, G., Panetta, C., Donati, M., and Muscardin, L. (2015) Indolent subtype acral lentiginous melanoma with long radial growth phase: a dermatopathological pitfall. *Am J Dermatopathol* **37**(11): 873–4.
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- Kim, J.Y., Choi, M., Jo, S.J., Min, H.S., and Cho, K.H. (2014) Acral lentiginous melanoma: indolent subtype with long radial growth phase. *Am J Dermatopathol* **36**(2): 142–7.

Melanoma of the nail bed



Atypical melanocytes spreading throughout the basal layer of the nail bed



MALIGNANT MELANOMA

Kwon, I.H., Lee, J.H., and Cho, K.H. (2004) Acral lentiginous melanoma in situ: a study of nine cases. *Am J Dermatopathol* **26**(4): 285–9.

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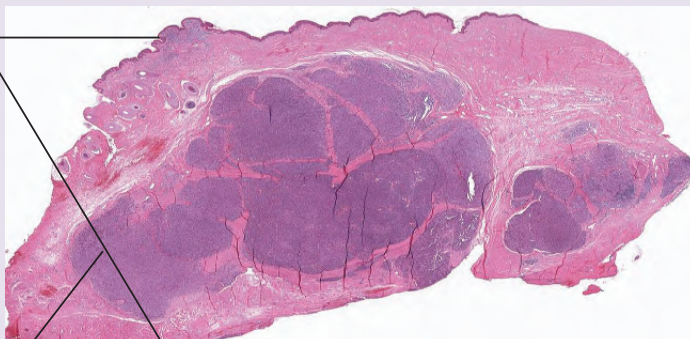
Variant: Melanoma in Large Congenital Melanocytic Nevus (LCMN)

Multiple nodular melanomas in LCMN (left)

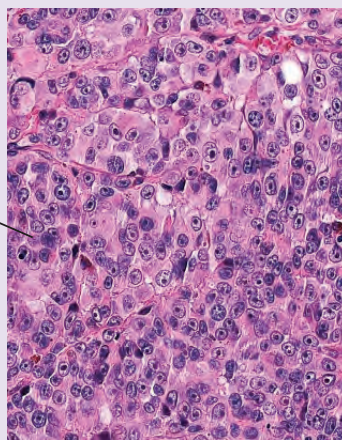
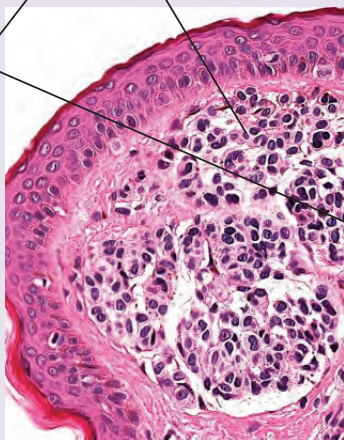
LCMN: partial removal of heavily pigmented areas (right)



Preexisting congenital nevus



Foci of nodular melanoma within congenital nevus



MALIGNANT MELANOMA

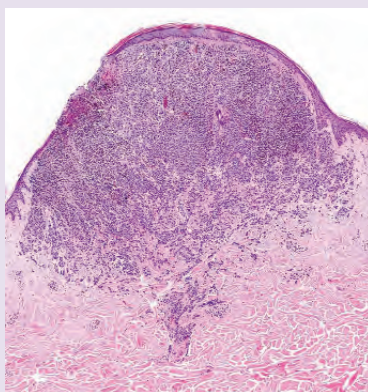
Cl: In large congenital melanocytic nevi (>20 cm) especially areas with dark pigmentation bear a high risk for the development of melanoma.

Hi: Corresponds to the changes in common types of melanomas.

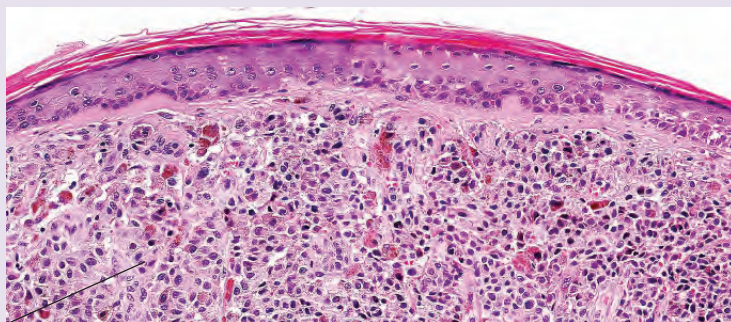
Variant: Cutaneous Metastasis of Melanoma

Multiple pigmented cutaneous metastases (left)

Cutaneous metastasis, non epidermotropic (right)

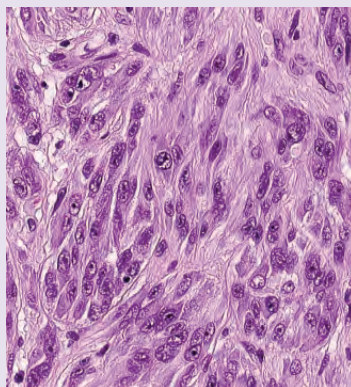
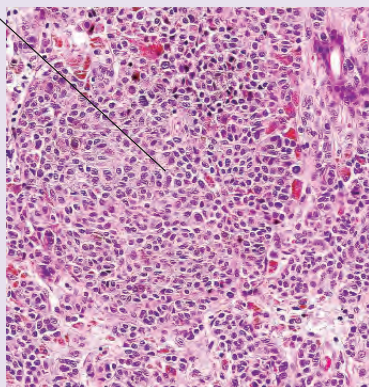


Lack of epidermotropism with subepidermal grenz zone



Atypical melanocytes

Atypical melanocytic spindle cells (right)



Cl: Pigmented or amelanotic skin-colored cutaneous and subcutaneous papules and nodules.

Hi:

- Atrophy of the epidermis
- Nodular proliferation of atypical melanocytes in the (upper) dermis
- Lacking or only focal epidermotropism of tumor cells

SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA

- Variable shapes of tumor cells, including balloon cells and spitzoid spindle cells
- Mitotic activity and melanin production variable

DD: Common (dermal) nevus; dermal Spitz nevus; cellular blue nevus.

References

Murali, R., Zannino, D., Synnott, M., McCarthy, S.W., Thompson, J.F., and Scolyer, R.A. (2011) Clinical and pathological features of metastases of primary cutaneous desmoplastic melanoma. *Histopathology* **58**(6): 886–95.

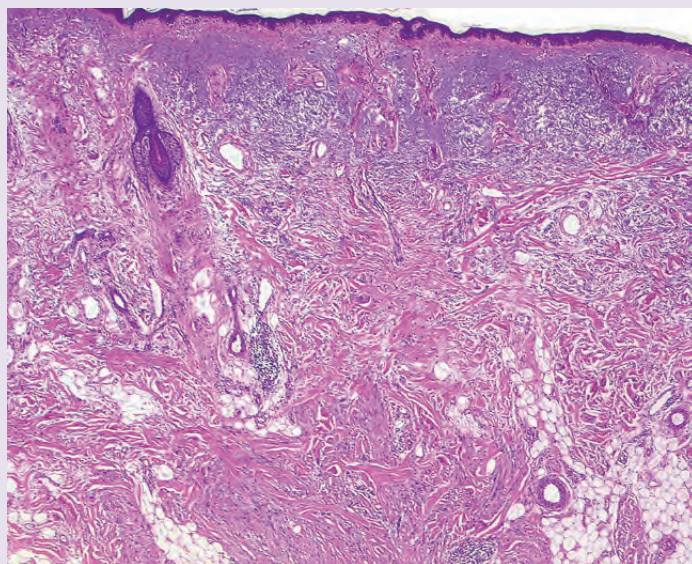
Plaza, J.A., Torres-Cabala, C., Evans, H., Diwan, H.A., Suster, S., and Prieto, V.G. (2010) Cutaneous metastases of malignant melanoma: a clinicopathologic study of 192 cases with emphasis on the morphologic spectrum. *Am J Dermatopathol* **32**(2): 129–36.

Special Histological Features of Malignant Melanoma

- Minimal deviation melanoma
- Melanoma ex naevo
- Neurotropic melanoma
- Nevus-like (nested) melanoma

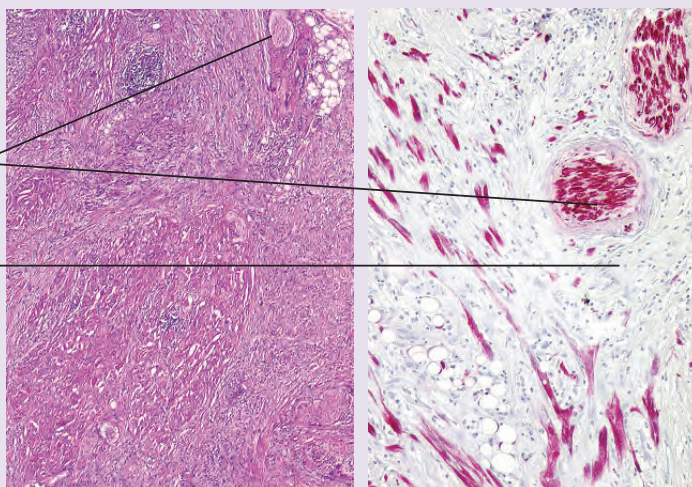
Neurotropic Melanoma

Diffuse infiltration of melanocytes in all levels of the dermis



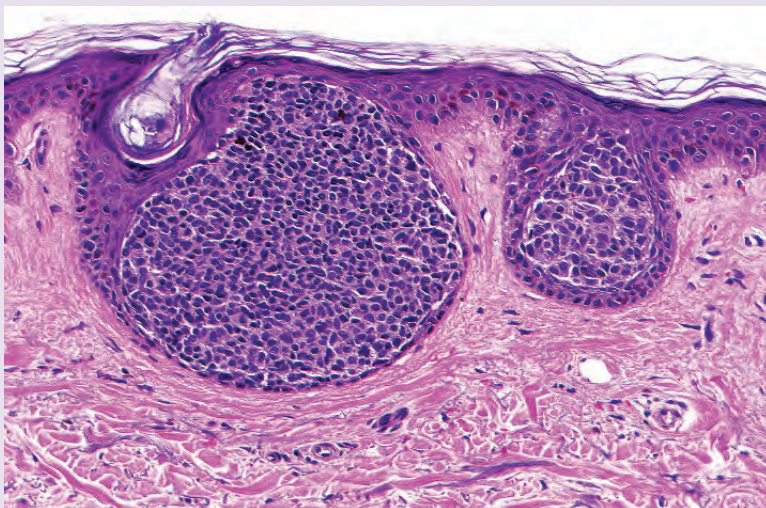
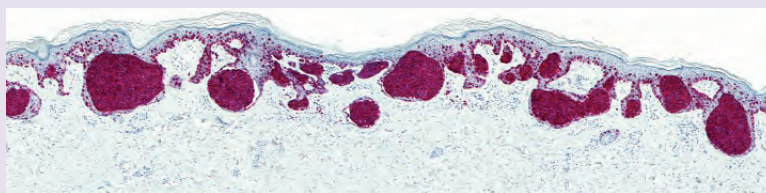
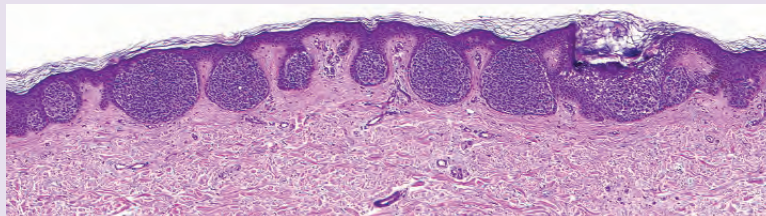
Nerve

Melanocytes, spreading along S100 positive peripheral nerve structures



SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA**Nevus-Like (Nested) Melanoma**

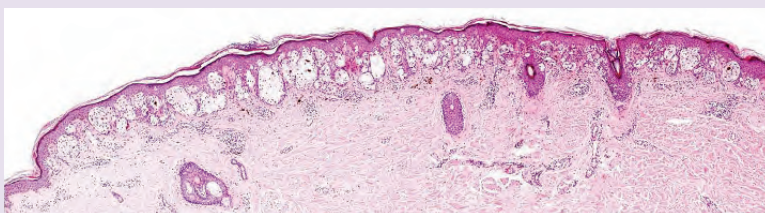
Intraepidermal nests of atypical melanocytes (top and bottom). HMB45 positive cells intraepidermal single and in nests (mid)

**Variant: Balloon Cell Melanoma**

CI: Clinical features of this rare variant correspond to common melanomas.

Variant: Balloon Cell Melanoma

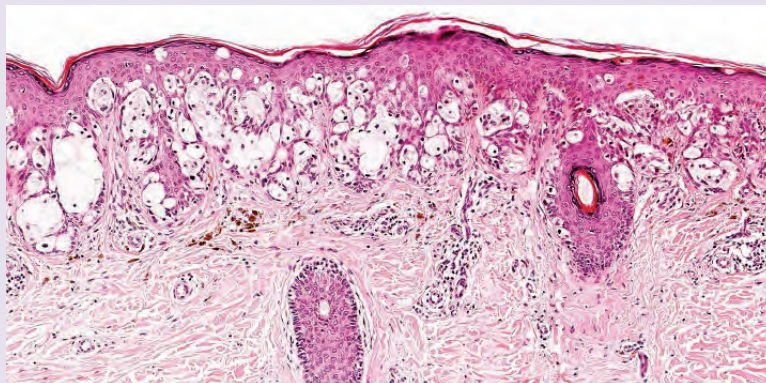
Large atypical melanocytes with abundant clear cytoplasm ("balloon cells") within the basal layer, at the junction and in the papillary dermis



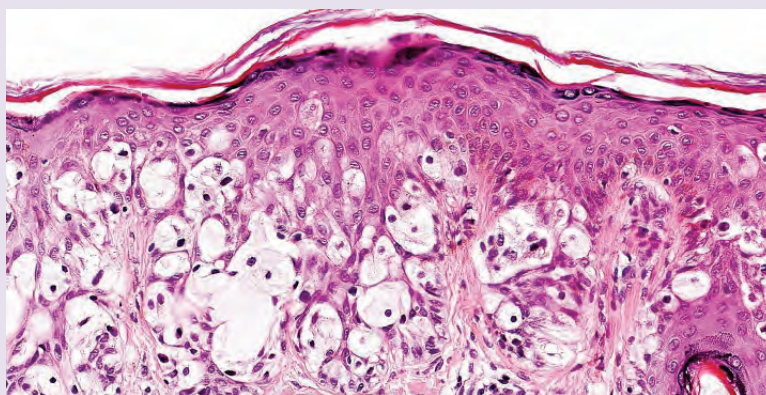
SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA

Variant: Balloon Cell Melanoma

Melanocytic nests of various sizes and shapes



Atypical melanocytes in solitary and nested arrangement, at the basal layer and above



Hi: Large melanocytes with broad cytoplasm (“balloon cells”) are the hallmark of this type of melanoma.

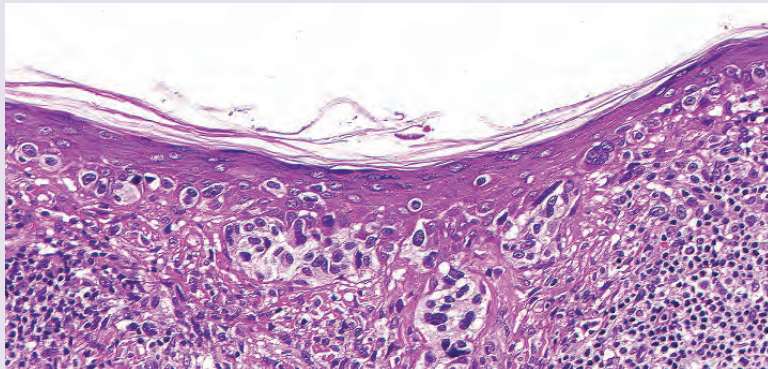
DD: Other clear cell tumors; xanthoma.

References

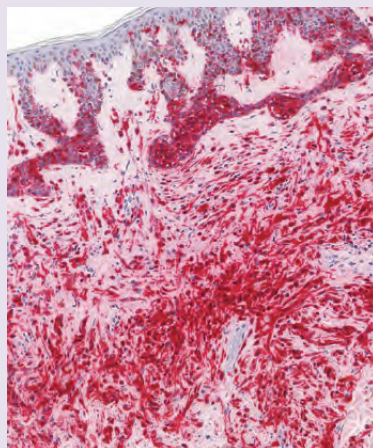
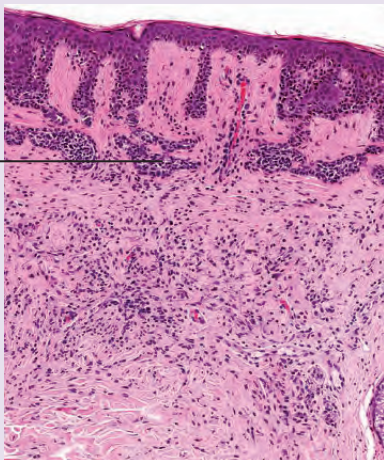
- Chavez-Alvarez, S., Villarreal-Martinez, A., Miranda-Maldonado, I., Ocampo-Candiani, J., and Garza-Rodriguez, V. (2017) Balloon cell melanoma and its metastasis, a rare entity. *Am J Dermatopathol* **39**(5): 404–11.
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- Northcutt, A.D. (2000) Epidermotropic xanthoma mimicking balloon cell melanoma. *Am J Dermatopathol* **22**(2): 176–8.

SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA**Variant: Desmoplastic Malignant Melanoma (DMM)**

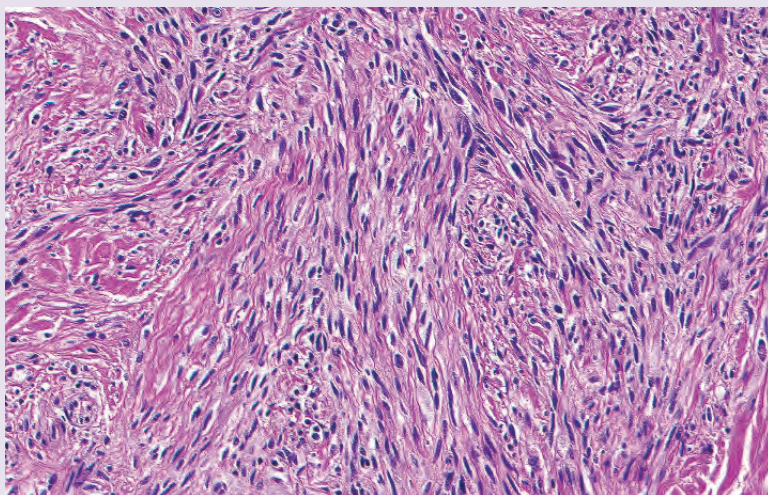
Overlying LMM showing
intraepidermal
nests of atypical
melanocytes



S100 stain
(right)



Proliferation of
spindle-shaped
melanocytes
(left and
bottom)



SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA

Cl: Clinical features correspond to common melanomas. However, there are hypopigmented variants of DMM that simulate the morphology of a scar, basal cell carcinoma, or dermatofibroma. Association with lentigo maligna melanoma is not uncommon.

Hi:

- Regular epidermis or overlying lentigo maligna melanoma
- Scar-like fibrotic stroma often simulating dermatofibroma
- Hypocellular variants of DMM resemble scars, albeit with a stroma positive for p75, WT1, and alpha smooth muscle actin (stromal myofibroblasts)
- Diffuse proliferation of amelanotic spindled melanocytes, positive for S100 and SOX10
- Dermal melanocytes are negative for MiTF, HMB45, and Melan A
- Tumor cells of DMM are p53-positive in contrast to neurofibroma with p53-negative Schwann cells
- Focal pleomorphism, low mitotic activity
- Cellular variants showing overlap with spindle cell melanoma
- Neurotropism is a common feature

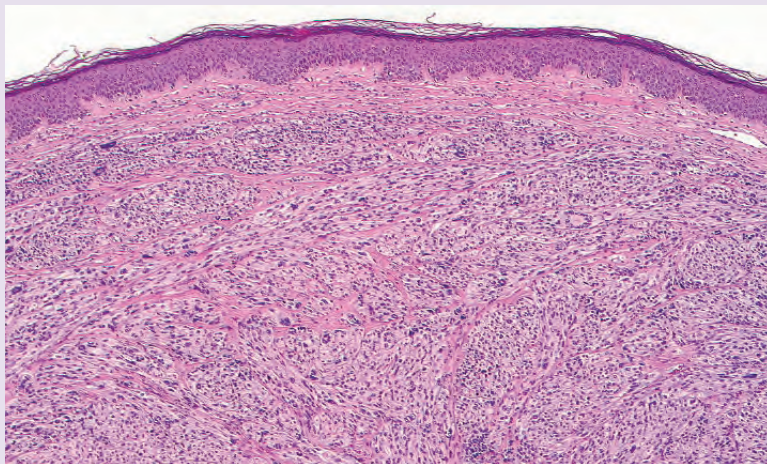
DD: Other spindle cell tumors; scar; desmoplastic nevus; neurofibroma; dermatofibroma; malignant peripheral nerve sheath tumor showing characteristic lack of nuclear expression of H3K27me3 (methylation marker); desmoplastic Spitz nevus.

References

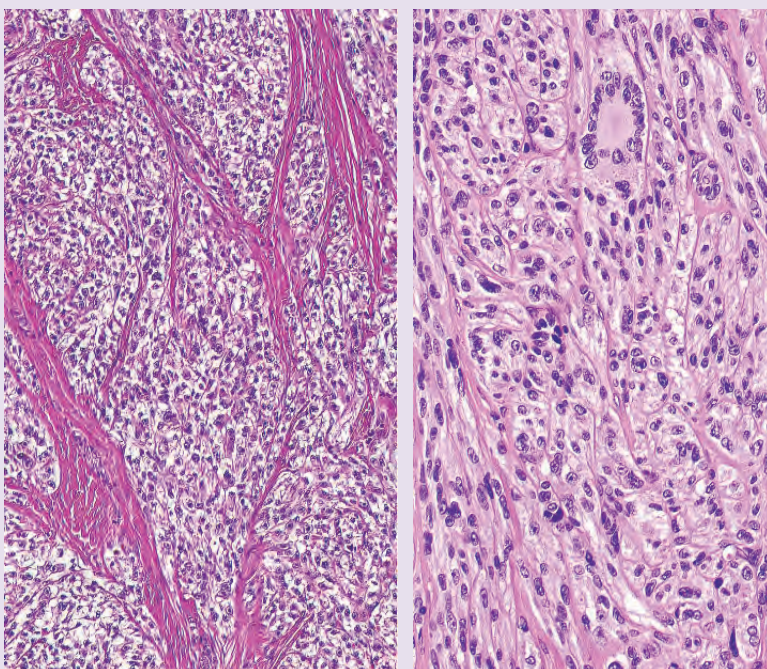
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SPECIAL HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA**Differential Diagnosis: Clear Cell Sarcoma (Melanoma of Soft Parts)**

Dermal clear cell infiltrate, non epidermotropic fascicles and multinucleate giant cells.



Interlacing fascicles (left) and clear cells with multinucleated cells (right)



This rare tumor nosologically is considered to be a clinicopathological entity originating from soft tissue in association with tendons and aponeuroses.

Cl: Deep, slowly growing tumor, preferentially involving the foot. Local recurrences and distal metastases occur.

Hi:

- Well-circumscribed dermal tumor
- Nests of tumor cells with eosinophilic granular cytoplasm
- Fibrous septae between tumor nests
- Multinucleated giant cells
- Melanin may be present

SPECIAL LOCALISATIONS OF MALIGNANT MELANOMA

Immunohistochemistry: Vimentin, S-100 protein, HMB45, MART-1 are expressed in most tumor cells.

DD: Metastatic melanoma; spindle cell melanoma; Spitz nevus; cellular blue nevus; fibrosarcoma; nerve sheath tumor.

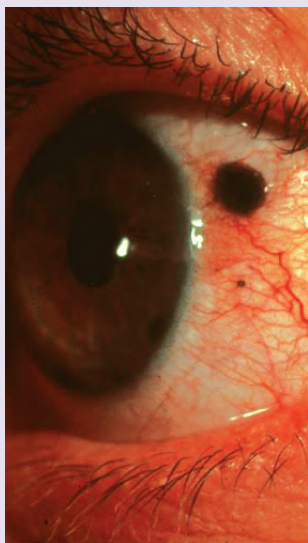
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- Mooi, W.J., Deenik, W., Peterse, J.L., and Hogendoorn, P.C. (1995) Keratin immunoreactivity in melanoma of soft parts (clear cell sarcoma). *Histopathology* **27**(1): 61–5.
- Warner, T.F., Hafez, G.R., Padmalatha, C., and Lange, T.A. (1983) Acral lentiginous melanoma simulating "clear cell sarcoma of tendon and aponeuroses". *J Cutan Pathol* **10**(3): 193–200.

Special Localisations of Malignant Melanoma

- Conjunctiva
- Male genitalia; orificium urethrae
- Oral mucous membrane and palate

Special Localisations of Malignant Melanoma



Conjunctiva



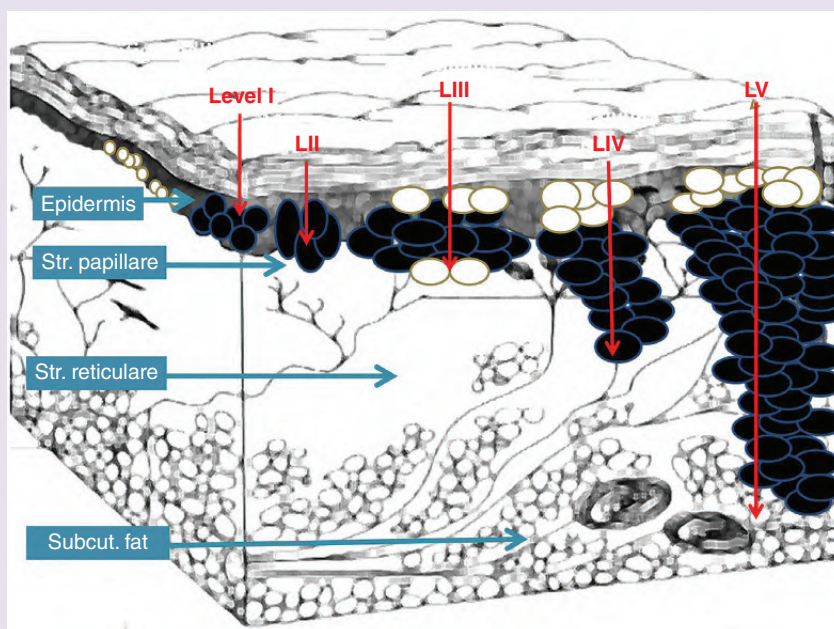
Orificium urethrae



Oral palate

MALIGNANT MELANOMA

Tumor Thickness and Levels



Level I Tumor cells in epidermis; Level II Tumor cells in papillary dermis; Level III Tumor cells filling papillary dermis; Level IV Tumor cells in reticular dermis; Level V Tumor cells in subcutaneous fat

The major independent risk factor in malignant melanoma is tumor thickness, measured with an ocular micrometer as distance from the stratum corneum to the deepest tumor cell at the base of the tumor, and given in mm Breslow depth.

As a rule of thumb, there is an almost linear correlation between the measured Breslow depth and the tumor level, which is also reflected in the AJCC staging classification (pT1 < 1 mm; pT2 up to 2 mm; pT3 up to 4 mm; pT4 > 4 mm).

- Level I Tumor cells in the epidermis
- Level II Tumor cells in the papillary dermis
- Level III Tumor cells filling the papillary dermis
- Level IV Tumor cells in the reticular dermis
- Level V Tumor cells in the subcutis

References

- Balch, C.M., Gershenwald, J.E., Soong, S. J., et al. (2009) Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* **27**(36): 6199–206.
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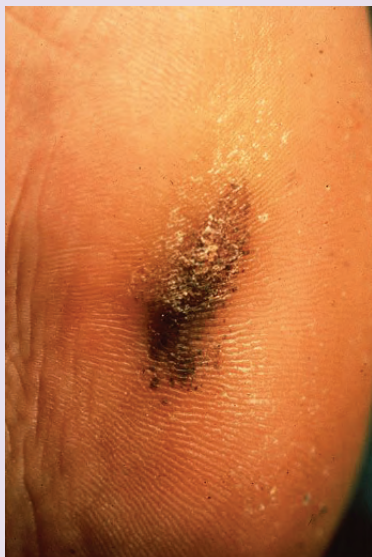
Common Clinical Differential Diagnoses of Malignant Melanoma

- Post-traumatic intracorneal thrombi (“black heel”)
- Pigmented basal cell carcinoma, pigmented Bowen’s disease
- Pigmented seborrheic keratosis (melanoacanthoma)
- Subungual hematoma
- Angioma or hematoma of the oral mucosa
- Angiokeratoma (see Chapter 6)

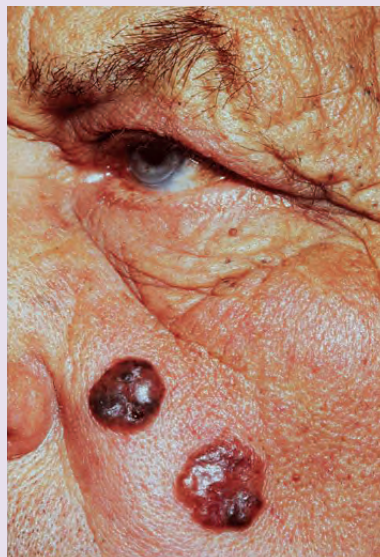
MALIGNANT MELANOMA

Common Clinical Differential Diagnoses of Malignant Melanoma

Black heel (left)



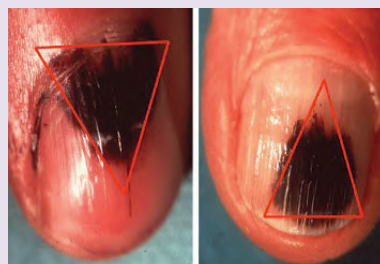
Pigmented BCC (right)



Seborrheic keratosis (left)



Angioma of the oral mucosa (bottom right)



Acrolentiginous melanoma (left) and Subungual hematoma (right)



CHAPTER 5

Connective Tissue

CHAPTER MENU

Nevi

Connective Tissue Nevus (Shagreen Patch; Cobblestone Nevus; Nevus Collagenicus)

Fibrous Neoplasms

Soft Fibroma (Skin Tag; Acrochordon)

Perifollicular Fibroma (Fibrofolliculoma; Trichodiscoma)

Variant: Sclerotic Fibroma (Plywood Fibroma; Storiform Collagenoma)

Variant: Fibrous Papule of the Nose

Variant: Pleomorphic Sclerosing Fibroma with Multinucleated Cells

Keloid

Infantile Digital Fibromatosis (Inclusion Body Fibromatosis; Recurring Digital Fibrous Tumor of Children; Reye's Tumor)

Malformations with Supernumerary Tissue Elements

Supernumerary Digit (Rudimentary Digit; Rudimentary Polydactyly)

Differential Diagnosis: Acral Acquired Fibrokeratoma

Accessory Tragus (Preauricular Tag)

Accessory Nipple (Ectopic Breast; Polythelia)

Fibrohistiocytic Neoplasms

Dermatofibroma (Benign Fibrous Histiocytoma; Fibroma Durum; Sclerosing Hemangioma)

Dermatofibrosarcoma Protuberans

Variant: Pigmented Dermatofibrosarcoma Protuberans (Bednar's Tumor)

Variant: Giant Cell Fibroblastoma

Pleomorphic Dermal Sarcoma (PDS)

Miscellaneous Tumors

Epithelioid Sarcoma

Dermatomyofibroma

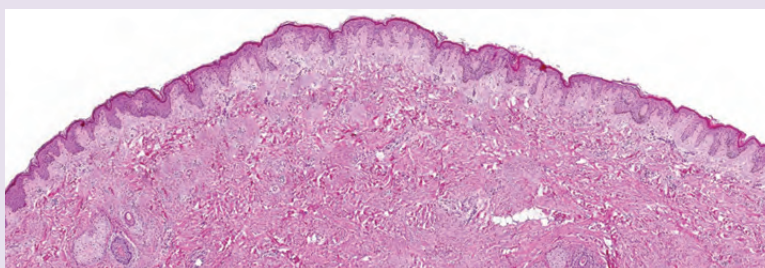
Nevi

Connective Tissue Nevus (Shagreen Patch; Cobblestone Nevus; Nevus Collagenicus)

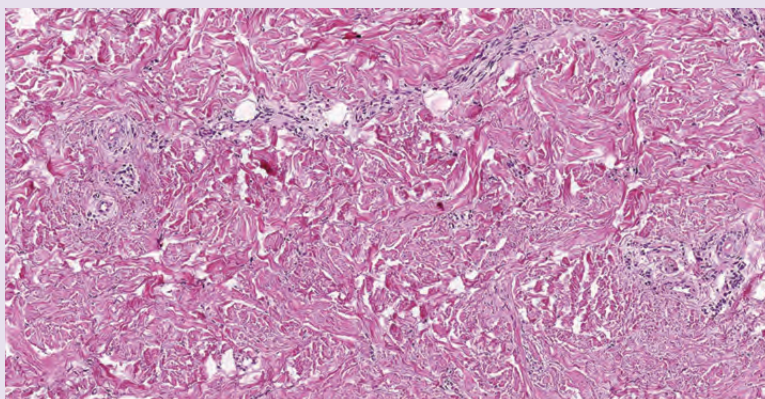
Multiple coalescent soft nodules on the buttock



Normal epidermis; broad dermis



Densely packed collagenous fibres without parallel arrangement



These lesions are frequently associated with syndromes, such as tuberous sclerosis or Buschke-Ollendorff syndrome.

Cl: Skin-colored solitary or multiple coalescent soft plaques or nodules in linear or zosteriform arrangement at birth or later in life, preferentially localized in the lumbosacral region.

Hi: This type of nevus is a simulator of “normal skin.”

- Normal epidermis
- Paucicellular thickening of the dermis
- Homogeneous interwoven thickened and densely packed bundles of collagen
- No proliferation of fibroblasts
- Variable amount of elastic fibers
- No parallel arrangement of fascicles as seen in scar tissue or keloids

DD: Normal skin; dermatofibroma; pseudoxanthoma elasticum; scar tissue; dermatofibrosis lenticularis disseminata (Buschke–Ollendorff).

References

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- de Feraudy, S. and Fletcher, C.D. (2012) Fibroblastic connective tissue nevus: a rare cutaneous lesion analyzed in a series of 25 cases. *Am J Surg Pathol* **36**(10): 1509–15.
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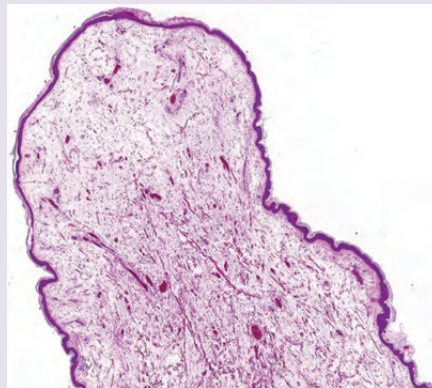
Fibrous Neoplasms

Soft Fibroma (Skin Tag; Acrochordon)

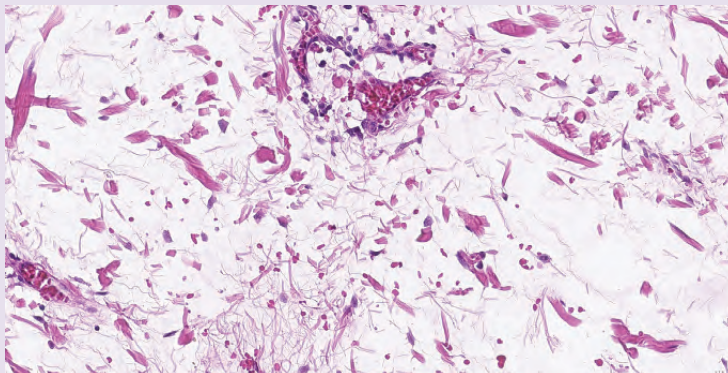
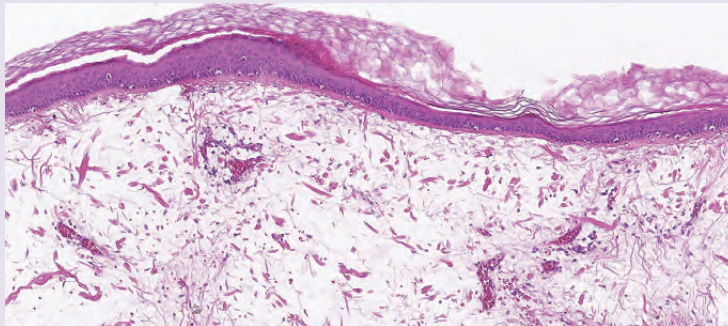
Multiple pedunculated soft fibromas in the axilla



Soft fibroma with myxoid alteration of stroma (right)



Loosely packed collagenous tissue amidst an unusually mucin-rich stroma (mid and bottom)



CI: Common lesion in middle-aged or elderly individuals, preferentially in large skinfolds but also at any other localisation. Skin-colored or variably pigmented polypous or papular soft lesions, sometimes pedunculated. When the shaft of the lesion is twisted, infarction with necrosis and black discoloration can occur.

Hi:

- Exophytic polypous lesion
- Epidermis acanthotic papillomatous, normal or flattened
- Stroma composed of collagen tissue showing variable texture, loosely to densely packed
- Variable amount of fat tissue and small vessels
- Elastic fibers may be reduced

DD: Fibrolipoma (variant); fibroepithelial polyp; seborrheic keratosis; nevus lipomatosus; angiofibroma; involuted melanocytic nevus

References

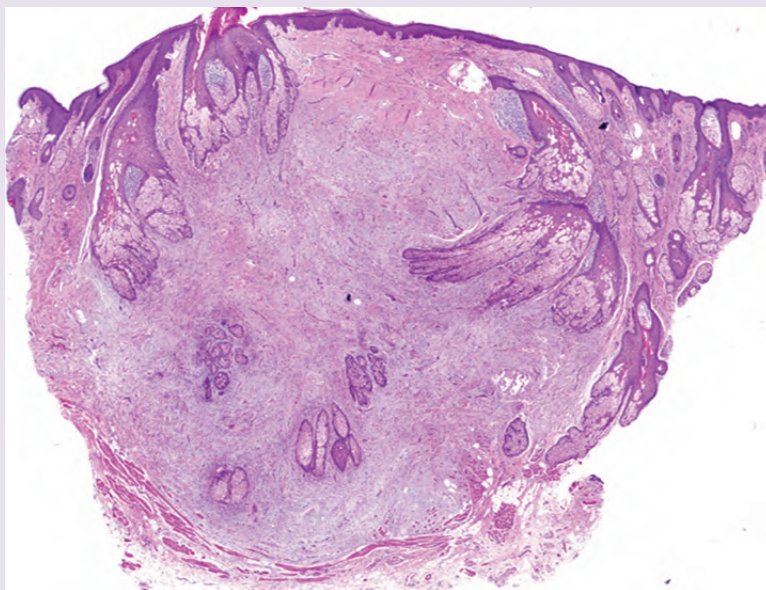
- Paredes, B.E. and Mentzel, T. (2011) Atypical lipomatous tumor/"well-differentiated liposarcoma" of the skin clinically presenting as a skin tag: clinicopathologic, immunohistochemical, and molecular analysis of 2 cases. *Am J Dermatopathol* **33**(6): 603–7.
- Tan, O., Atik, B., and Bayram, I. (2005) Skin tag. *Dermatology* **210**(1): 82–3.

Perifollicular Fibroma (Fibrofolliculoma; Trichodiscoma)

Papular lesions on cheek (left) and nose (right)

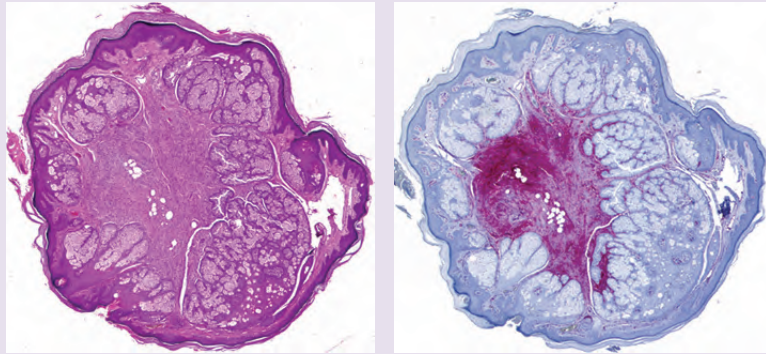


Downward proliferation of fibrous tissue including central pilosebaceous structures



Perifollicular Fibroma (Fibrofolliculoma; Trichodiscoma)

Horizontal cut through spindle cell predominant trichodiscoma. H&E (left) and CD34 (right)



Cl: Perifollicular papules, solitary or multiple. Lesions are related to, if not identical with, trichodiscoma. Association with Birt–Hogg–Dubé syndrome, presenting as multiple flat white papules in the face.

Hi:

- Protuberant symmetrical papular tumor
- CD34-positive fibroblasts in the center, arranged in fascicles and strands
- Mucinous stroma
- Hyperplastic (“mitt-like”) sebaceous glands on both sides of the tumor
- Ostiofollicular vestiges may be present in the center
- Focal entrapment of adipocytes

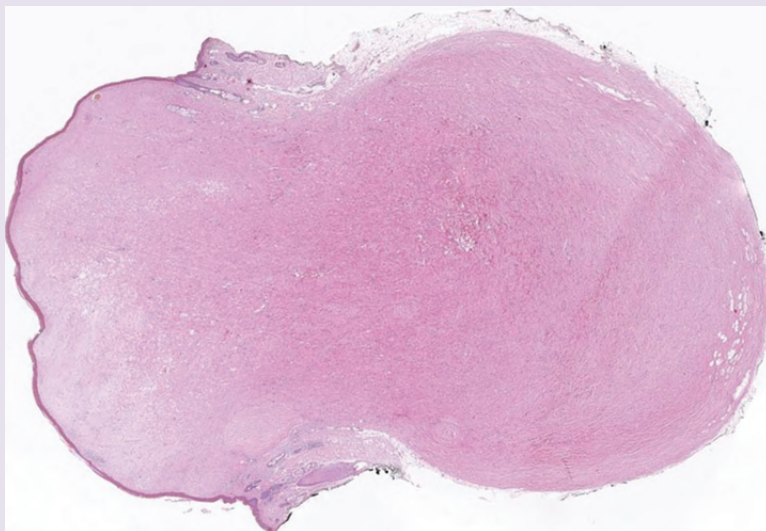
DD: Angiofibroma.

References

- Nam, J.H., Min, J.H., Lee, G.Y., and Kim, W.S. (2011) A case of perifollicular fibroma. *Ann Dermatol* **23**(2): 236–8.
- Misago, N., Kimura, T., and Narisawa, Y. (2009) Fibrofolliculoma/trichodiscoma and fibrous papule (perifollicular fibroma/angiofibroma): a reevaluation of the histopathological and immunohistochemical features. *J Cutan Pathol* **36**(9): 943–51.
- Shvartsbeyn, M., Mason, A.R., Bosenberg, M.W., and Ko, C.J. (2012) Perifollicular fibroma in Birt-Hogg-Dube syndrome: an association revisited. *J Cutan Pathol* **39**(7): 675–9.

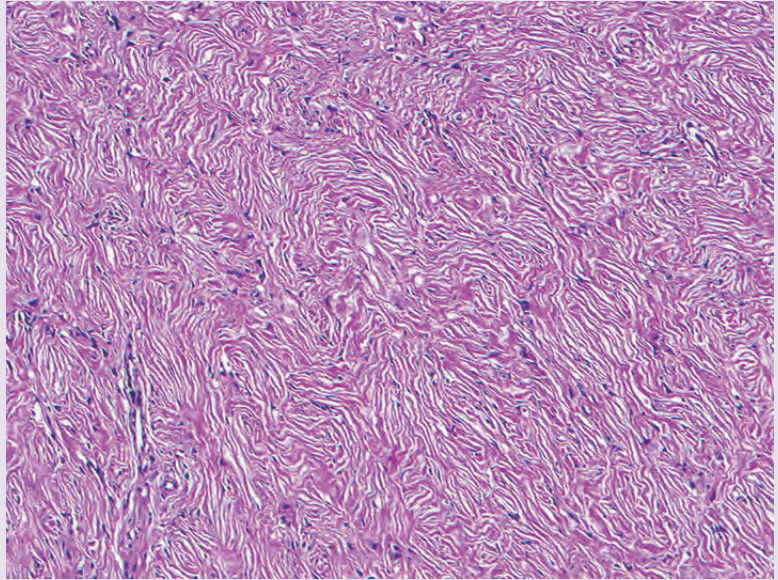
Variant: Sclerotic Fibroma (Plywood Fibroma; Storiform Collagenoma)

Dermal nodule with paucicellular fibrosis



Variant: Sclerotic Fibroma (Plywood Fibroma; Storiform Collagenoma)

Characteristic
“fingerprint” or
“plywood” pattern



Cl: Solitary lesion. Multiple lesions may occur in association with Cowden’s disease.

Hi: Symmetrical protuberant nodule with paucicellular CD34-positive fibroblastic proliferation embedded in a sclerotic whirl-like stroma (so-called “fingerprint” or “plywood” pattern).

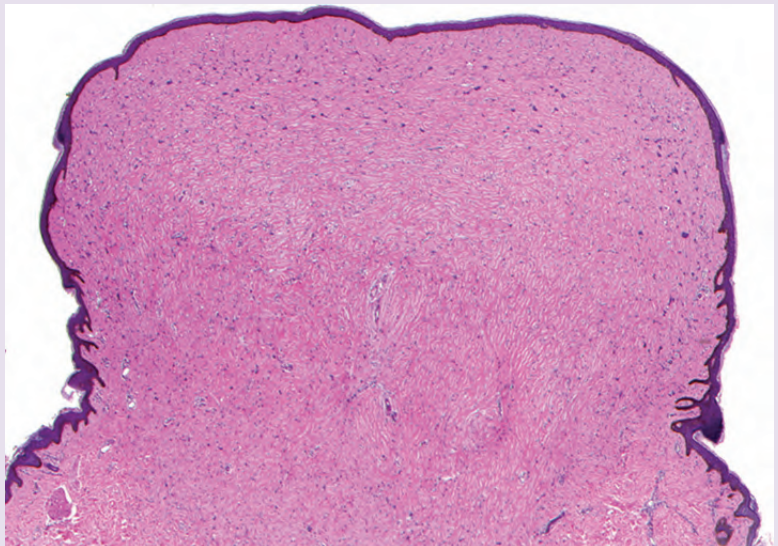
Variant: Fibrous Papule of the Nose

Cl: Skin-colored dome-shaped papule.

Hi: Connective tissue with some larger, stellate, spindle or bizarre cells. Often ectatic blood vessels.

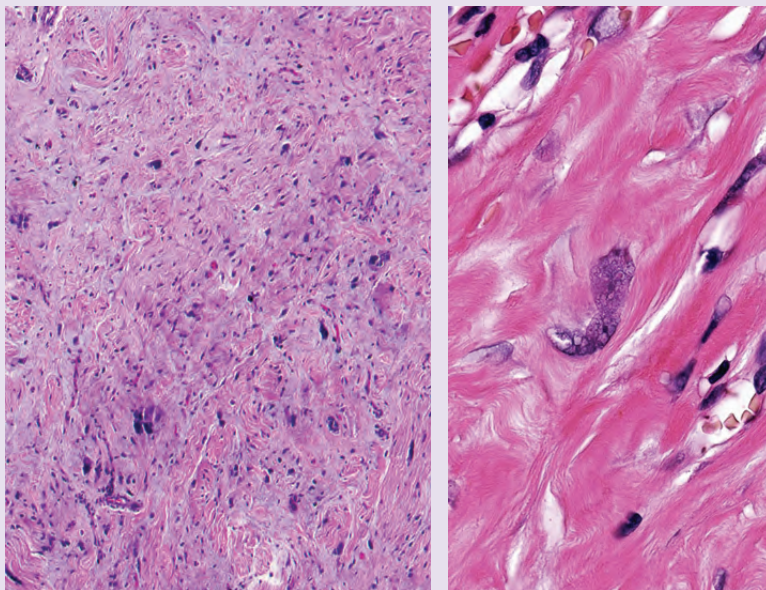
Variant: Pleomorphic Sclerosing Fibroma with Multinucleated Cells

Dermal nodule of
fibrous tissue



Variant: Pleomorphic Sclerosing Fibroma with Multinucleated Cells

Pleomorphic cells in a fibrous background



Cl: polypous nodule, resembling skin tag.

Hi: Pleomorphic stellate fibroblastic cells, negative for both CD34 and alpha smooth muscle actin.

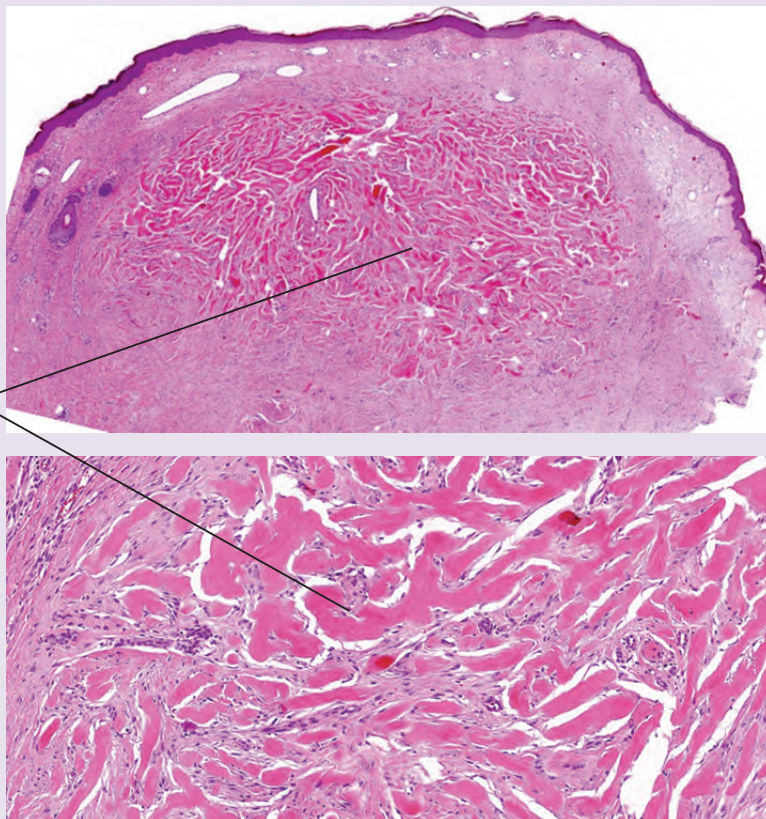
Keloid

Keloid on the upper arm (left) and breast (moulage) (right)



Keloid

Coarse
eosinophilic
collagen bundles



CI: In contrast to hypertrophic scars, keloids are well-circumscribed, slowly growing benign tumors, proliferating beyond margins of earlier tissue injury, burning, inflammatory condition, acne or surgery. Predilection for the head and neck, upper chest, and shoulder region of black individuals. The pruritic red firm tumors show a smooth surface.

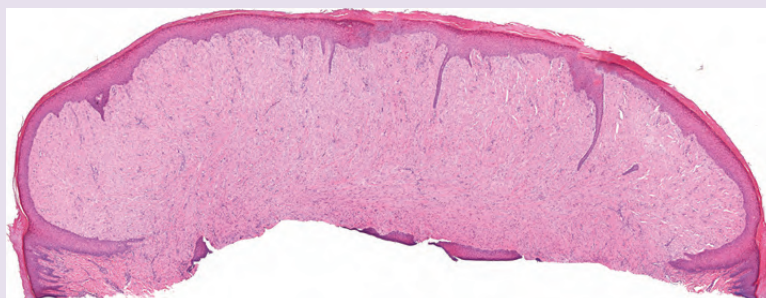
Hi:

- Epidermis normal or atrophic
- Broad hyalinized and sclerotic collagen bundles and fibroblasts
- Scarce inflammatory infiltrate

DD: Hypertrophic scar.

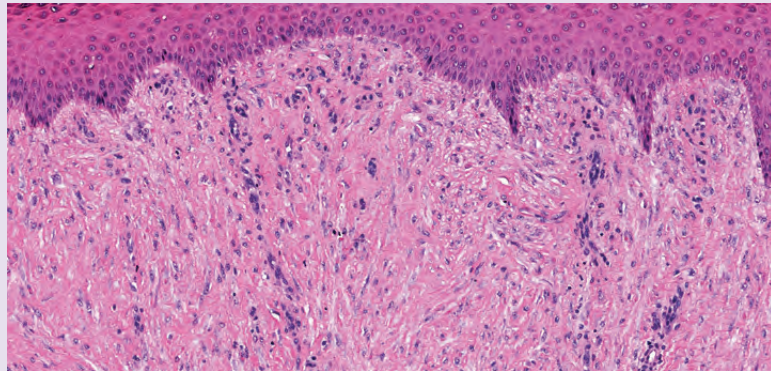
Infantile Digital Fibromatosis (Inclusion Body Fibromatosis; Recurring Digital Fibrous Tumor of Children; Reye's Tumor)

Dermal fibrous
tumor

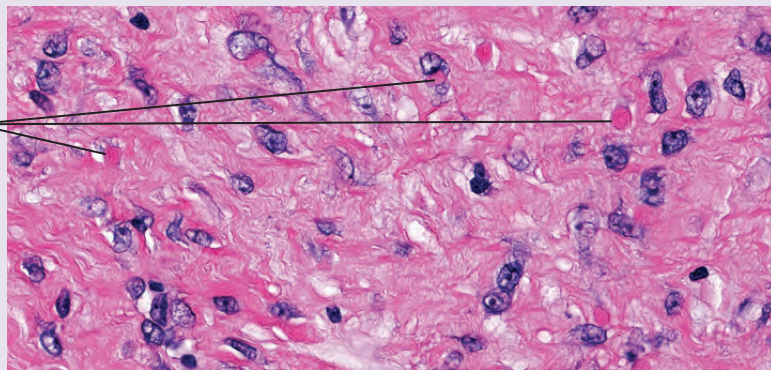


Infantile Digital Fibromatosis (Inclusion Body Fibromatosis; Recurring Digital Fibrous Tumor of Children; Reye's Tumor)

Spindle shaped fibroblasts and myofibroblasts



Eosinophilic inclusion bodies



Cl: Solitary, rarely multiple soft tumorous swelling on the fingers or toes, rarely in other localisations. Usually present at birth or shortly thereafter but occurrence in adults has been reported. Tendency to spontaneous regression.

Hi:

- Poorly circumscribed dermal tumor, extending into the subcutis
- Interlacing bundles of spindle-shaped fibroblasts and myofibroblasts, positive for actin and vimentin
- The eosinophilic inclusion bodies (accumulation of actin) within the cytoplasm of fibroblasts may be as large as erythrocytes

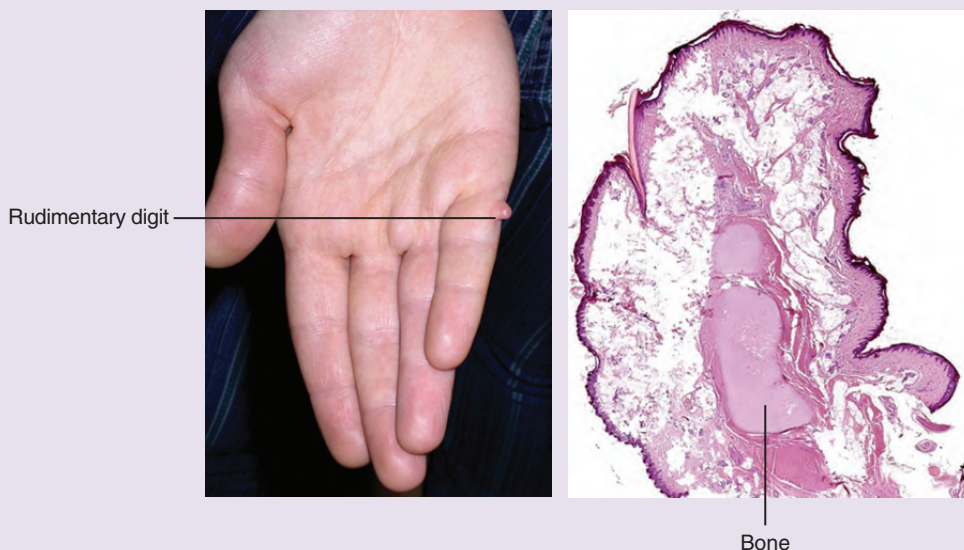
DD: Dermatofibroma.

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- Pettinato, G., Manivel, J.C., Gould, E.W., and Albores-Saavedra, J. (1994) Inclusion body fibromatosis of the breast. Two cases with immunohistochemical and ultrastructural findings. *Am J Clin Pathol* **101**(6): 714–18.
- Suryawanshi, P., Rekhi, B., and Jambhekar, N.A. (2010) Morphological spectrum of inclusion body fibromatosis: a rare case report. *Indian J Pathol Microbiol* **53**(4): 827–28.
- Viale, G., Doglioni, C., Iuzzolino, P., et al. (1988) Infantile digital fibromatosis-like tumour (inclusion body fibromatosis) of adulthood: report of two cases with ultrastructural and immunocytochemical findings. *Histopathology* **12**(4): 415–24.
- Zardawi, I.M. and Earley, M.J. (1982) Inclusion body fibromatosis. *J Pathol* **137**(2): 99–107.

Malformations with Supernumerary Tissue Elements

Supernumerary Digit (Rudimentary Digit; Rudimentary Polydactyly)



CI: These are congenital supernumerary rudimentary fingers, potentially composed of all elements of normal fingers, including bone, cartilage, nerves, and nail. Preferential localisation is the lateral side of the fifth digit, most frequently in black people.

Hi:

- Digital outgrowth
- Fibrous stroma
- Hypertrophic nerves
- Association with mature cartilage or bone

DD: Post-traumatic neuroma, digital fibrokeratoma; skin tag; pedunculated wart; fibroma; neurofibroma.

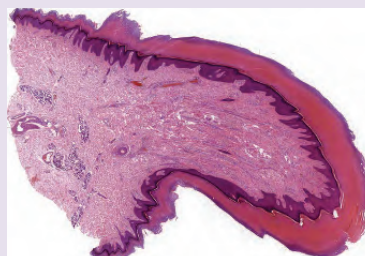
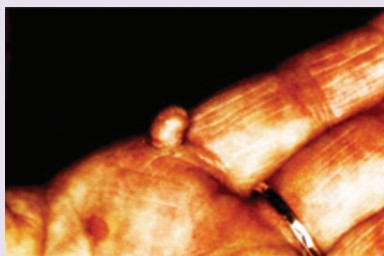
Reference

Kim, J., Zambrano, E.V., and McNiff, J.M. (2007) Congenital panfollicular nevus associated with polydactyly. *J Cutan Pathol* **34**(Suppl 1): 14–17.

Differential Diagnosis: Acral Acquired Fibrokeratoma

Filiform lesion on the hand (left)

Densely packed collagen tissue showing vertical orientation (right)



Cl: Solitary exophytic fibroma-like hyperkeratotic, narrow-based lesion, preferentially localized on the lateral side of the hands, sometimes also feet, fingers or toes. Preceding trauma may play an etiological role.

Hi:

- Exophytic filiform lesion
- Acanthosis and hyperkeratosis
- Proliferation of densely packed, hyalinized fibrous tissue with parallel orientation along the vertical axis
- No bone or cartilage

DD: Supernumerary digit; pedunculated wart; soft fibroma; dermatofibroma (histiocytoma);

angiofibroma; periungual fibroma (Koenen tumor, associated with tuberous sclerosis); superficial acral fibromyxoma (positive for CD34 and nestin).

References

- Bode, U. and Burg, G. (1978) [The acquired digital fibrokeratoma] *Hautarzt* **29**(12): 659–60.
- Kint, A. and Baran, R. (1988) Histopathologic study of Koenen tumors. Are they different from acquired digital fibrokeratoma? *J Am Acad Dermatol* **18**: 369–72.

Accessory Tragus (Preauricular Tag)

Preauricular
polypous
papule (left)



Cartilage
Vellus hair
follicles

CI: Inborn preauricular pedunculated, polypous skin-colored nodule or papule. Association with various syndromes.

Hi:

- Normal epidermis

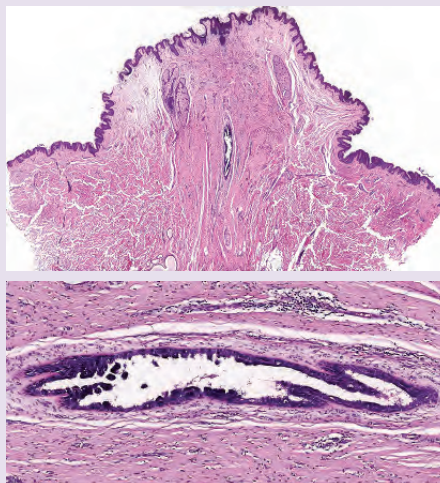
- Cartilage in the dermis and subcutaneous tissue
- Many vellus hair follicles

DD: Regular tragus; fibroepithelial lesion; hair follicle nevus.

Accessory Nipple (Ectopic Breast; Polythelia)

Bundles of smooth muscle (right top) around tubular structures with apocrine secretion (right bottom)

Pigmented papule with central dell (left)



CI: Solitary or multiple inborn reddish-brown papules with central dell, preferentially on the ventral trunk along the milk line.

Hi:

- Vertically oriented collagenous fibers
- Central follicle or dilated duct
- Bundles of smooth muscle

- Tubules with two-layered ductal apocrine epithelium
- Intraepidermal splaying of solitary CK7-positive Toker cells

DD: Dermal nevus; neurofibroma; leiomyoma.

Fibrohistiocytic Neoplasms

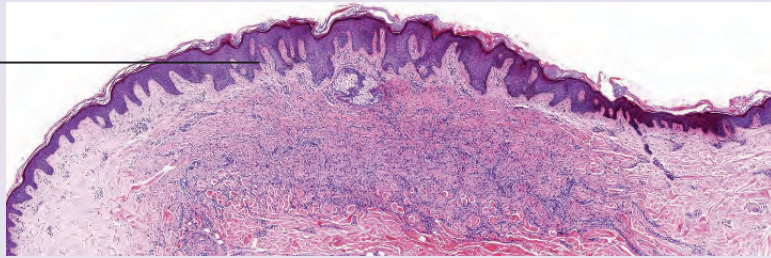
Dermatofibroma (Benign Fibrous Histiocytoma; Fibroma Durum; Sclerosing Hemangioma)

Dermatofibromas on the leg and in the face

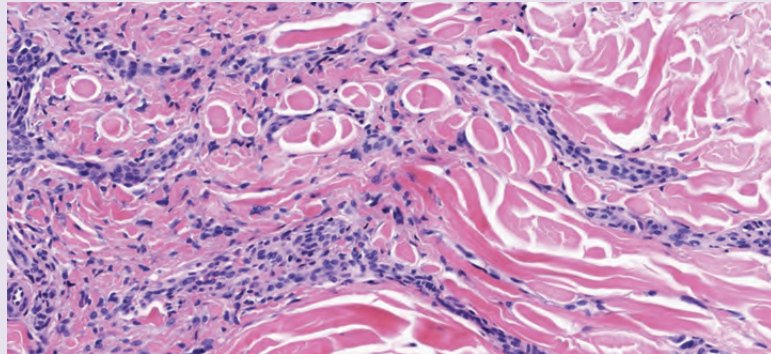


Dermatofibroma (Benign Fibrous Histiocytoma; Fibroma Durum; Sclerosing Hemangioma)

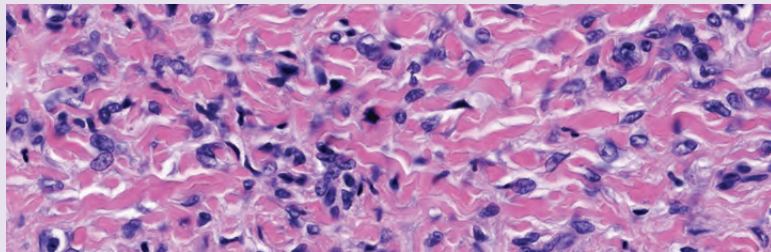
Acanthosis and papillomatosis on top of underlying mesenchymal proliferation



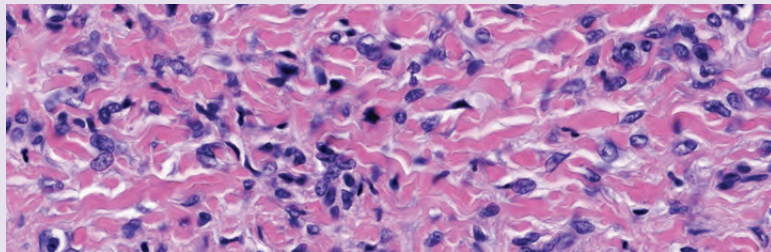
Diffuse proliferation of fibroblasts and histiocytes in the dermis



Broad "entrapped" collagen fibres: Radial spread of fibroblasts between collagen bundles



Proliferation of fibroblasts and histiocytes



CI: Common lesion preferentially on the extremities, presumably following insect bites or banal trauma. Solitary or multiple firm broad-based papules or nodules, which are red in the begin-

ning and turn skin colored or brownish after some time. Evolution into a slightly depressed scarring pigmented lesion. Several clinical variants of dermatofibroma exist.

VARIANTS

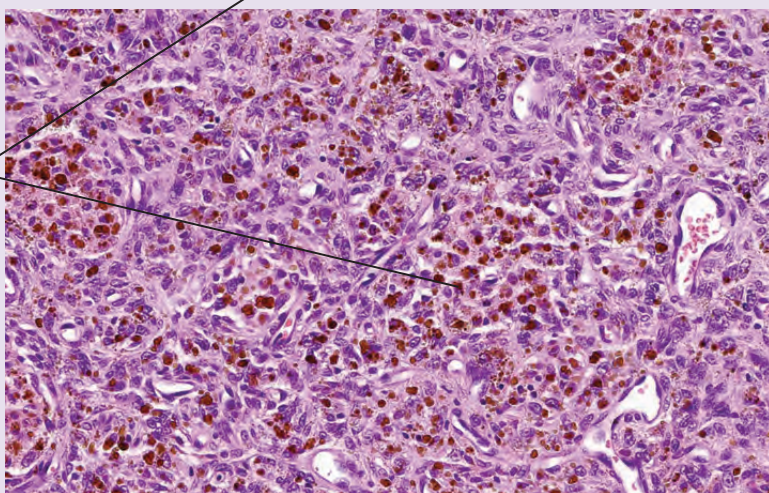
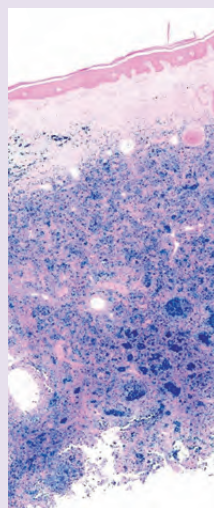
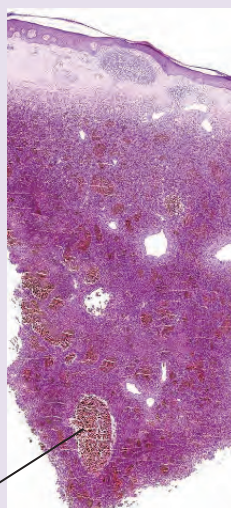
Sclerosing Hemangioma (Hemosiderotic Dermatofibroma)

Nodular dermatofibroma on the arm (left)

Dense proliferation of fibroblasts and histiocytes with pseudo-vascular spaces (mid) and siderophages (right)

Prussian blue staining of siderophages (right)

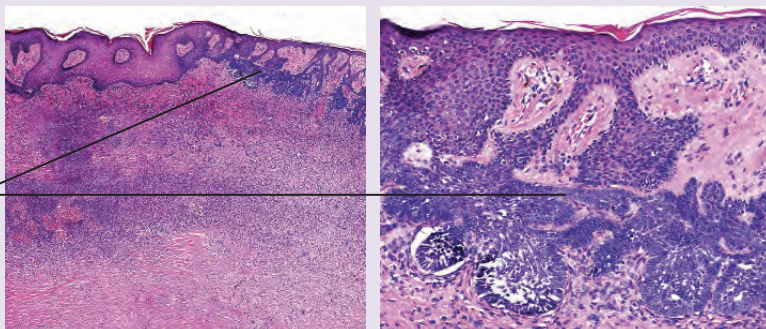
Pseudo-vascular (sinusoidal) spaces and sheets of siderophages



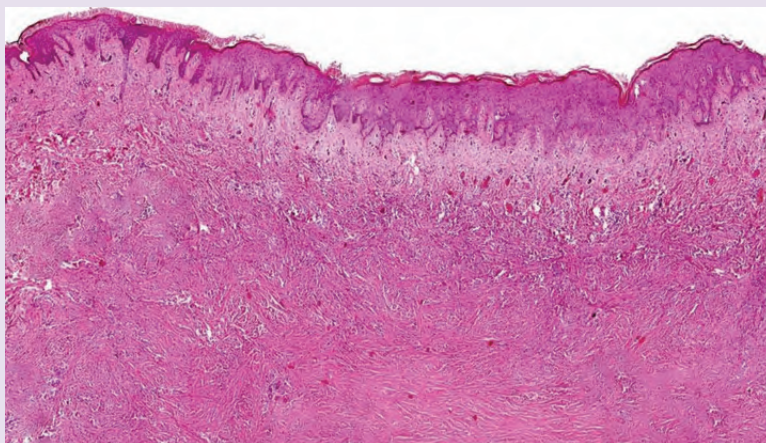
VARIANTS

Dermatofibroma (Histiocytoma) with Basaloid Proliferation of the Epidermis

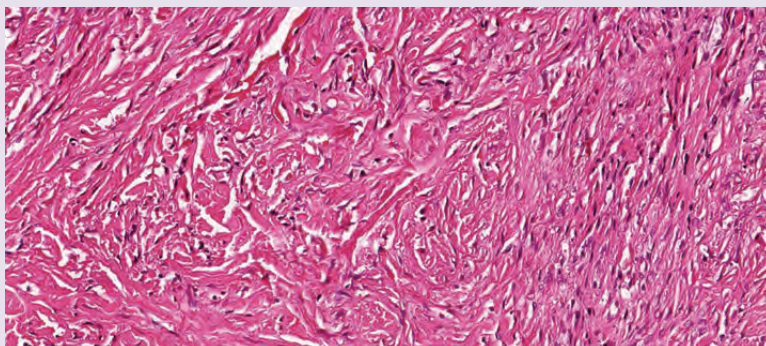
Induction of
basaloid
proliferation
imitating BCC

**Paucicellular Dermatofibroma**

Hyperplastic
epidermis



Paucicellular
fibrosis with
few embedded
fibroblasts and
histiocytes (mid
and bottom)

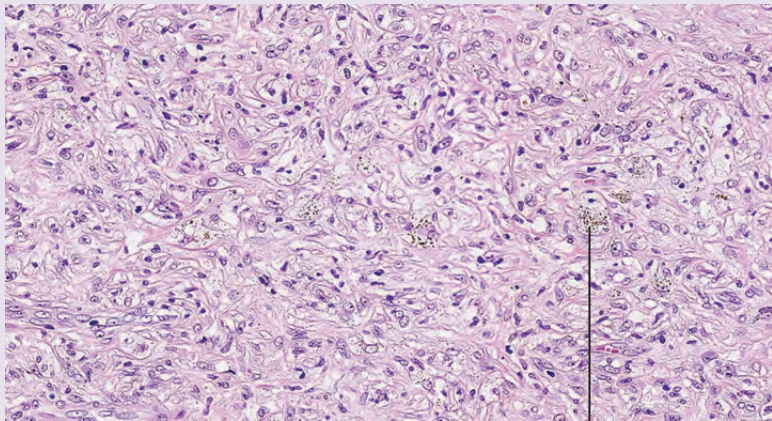
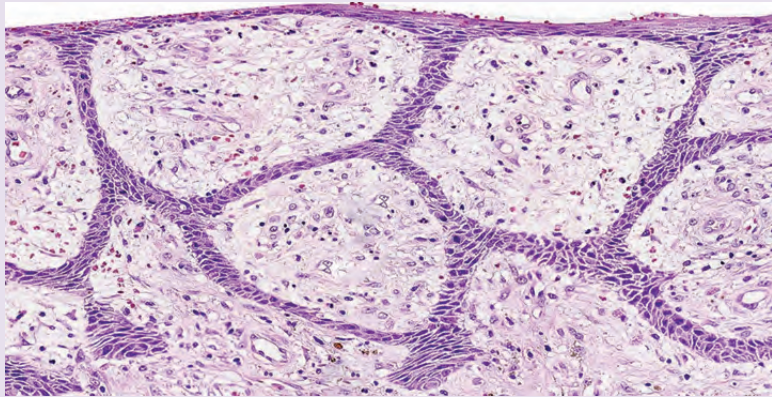
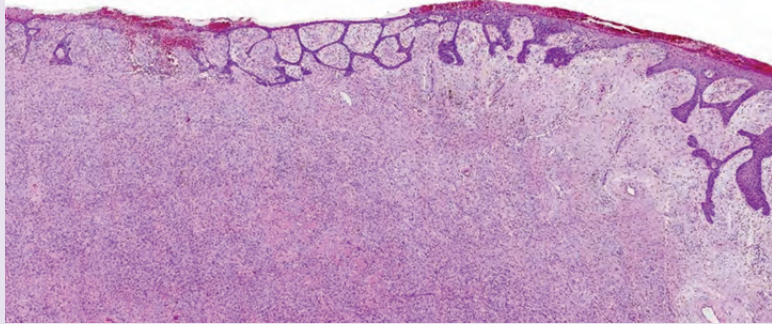


VARIANTS

Clear Cell Dermatofibroma

Branching
epithelial
proliferation (top
and mid)

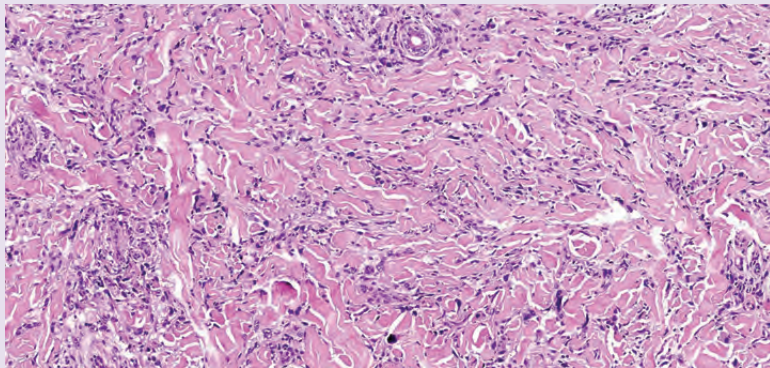
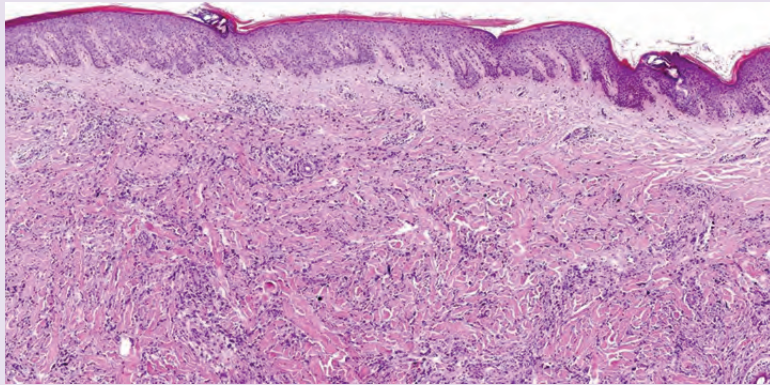
Proliferation of
large histiocytic
cells with ample
clear cytoplasm
(mid and bottom)



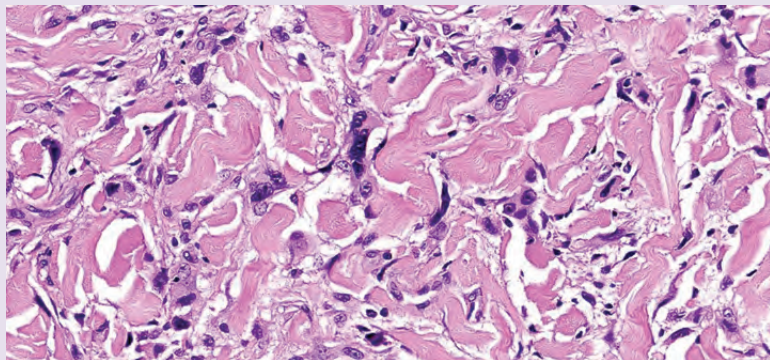
Siderophages

VARIANTS**Dermatofibroma with Monster Cells**

Large atypical cells amidst regular fibroblasts and histiocytes. Very few mitoses (top and mid)



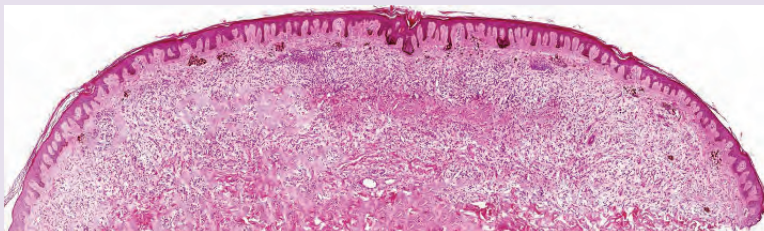
Marked hyperchromasia and pleomorphism of "monster cells"



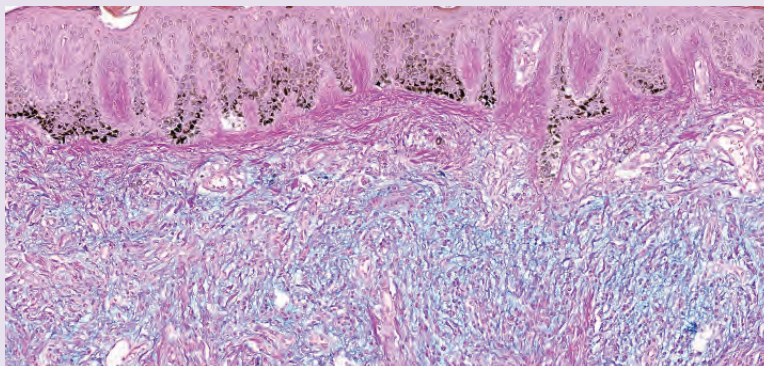
VARIANTS

Mucinous Dermatofibroma

Dome shaped tumor with acanthosis and papillomatosis

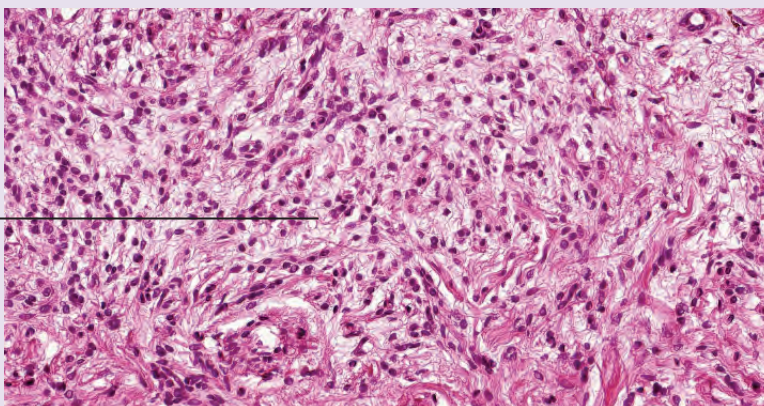


Basal hyperpigmentation



Increased amounts of mesenchymal mucin (Alcian blue)

Fat storing foam cells

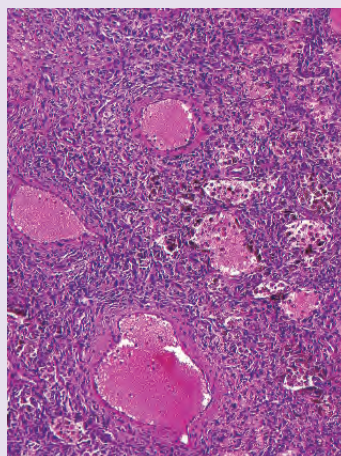
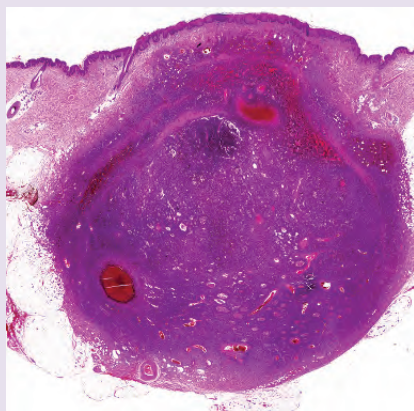


VARIANTS

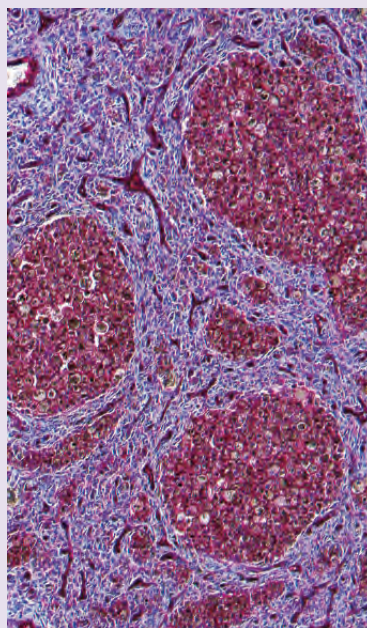
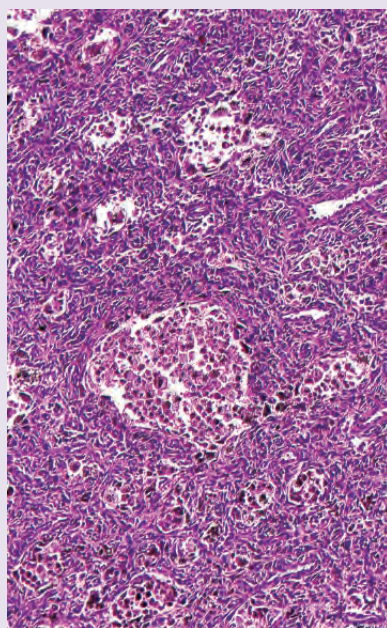
Aneurysmatic Dermatofibroma

Circumscribed
dermal
infiltrate (left)

Thrombosed
pseudovascular
spaces (right)



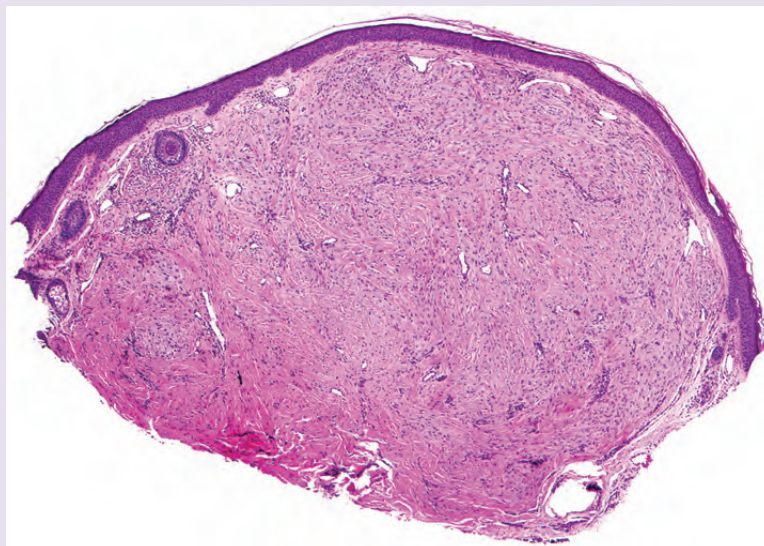
Granulation
tissue in
pseudovascular
spaces (left)
with CD68
positive
cells (right)



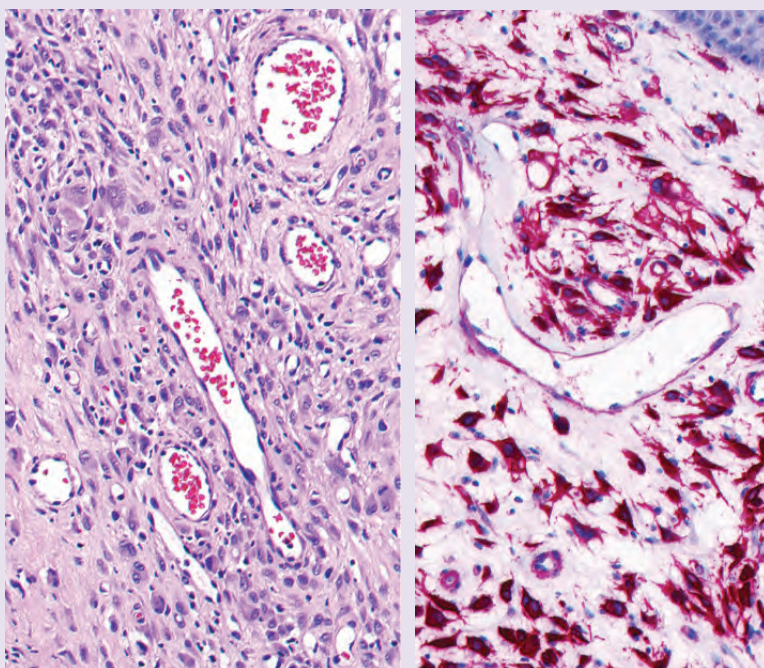
VARIANTS

Epithelioid Dermatofibroma

Richly vascularized well circumscribed dermal tumor



Epithelioid ALK-positive (right) histiocytes with ample eosinophilic cytoplasm. Many interspersed vessels (left)



Hi:

- Circumscribed acanthosis and papillomatosis
- Occasional basaloid buds extending from the acanthotic epidermis. They represent follicular induction resembling basal cell carcinoma
- In the dermis, proliferation of spindle cell fibroblasts with variable amount of newly formed collagen
- Lesions are circumscribed with irregular borders, which in the periphery show radial Indian file-like spread of fibroblasts between collagen bundles ("entrapped" broadened collagen bundles)
- Inflammatory infiltrate in the surrounding stroma, occasionally containing many plasma cells and eosinophils

- Initial lesions may have strong vascularization with extravasation of erythrocytes
- Later lesions may show xanthomatous changes with foamy histiocytes and macrophages
- Atrophy of the epidermis and paucicellular dense fibrous scarring tissue in the epidermis in resolving atrophic dermatofibromas
- Variants of common histiocytoma include cellular or large cellular histiocytomas with “monster cells,” paucicellular, aneurysmatic, clear cell, mucinous, xanthomatous, and epithelioid forms

DD: Melanocytic nevus; Spitz nevus; juvenile xanthogranuloma; nodular basal cell carcinoma; mastocytoma.

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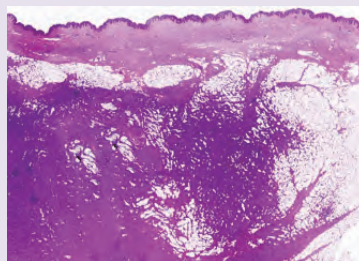
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Dermatofibrosarcoma Protuberans

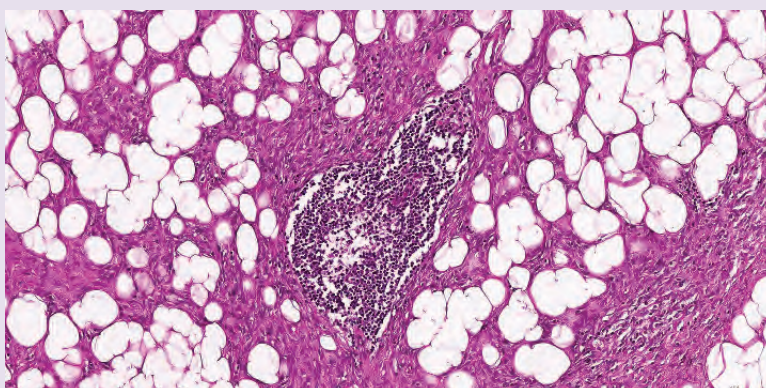
CI: Upper trunk, shoulder, head of young or middle-aged individuals are the most common localisations of this initially slowly growing, firm tumor with cutaneous and subcutaneous multiple confluent nodules. The overlying skin is red-brown with telangiectasias and shows a smooth surface without ulceration. Due to the mostly underestimated spread beyond clinically visible borders, removal is often incomplete and recurrences and final metastases occur frequently, occasionally with transformation into fibrosarcoma.

Dermatofibrosarcoma Protuberans

Large tumor composed of confluent plaques and nodules

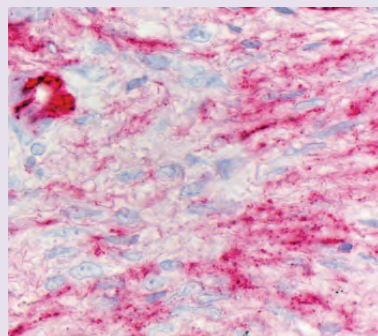
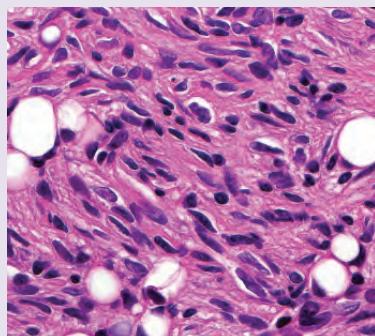


Proliferation of monomorphous spindle cells, and characteristic "entrapped" fat cells—producing a sieve-like pattern (right top and mid)



Monomorphous spindle cells (left)

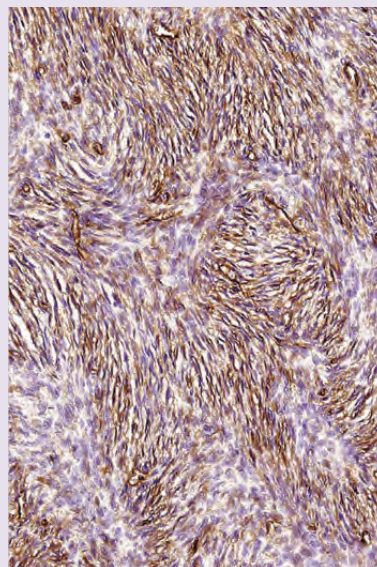
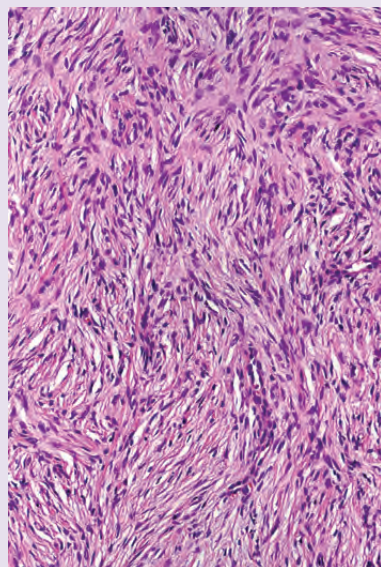
CD34-positive tumor cells (right)

**Hi:**

- Epidermal hyperplasia with hyperpigmentation of the stratum basale
- Dermal and subcutaneous tumor with poorly defined borders
- Sparing of the papillary dermis
- Monomorphous spindle cells with prominent nuclei
- Storiform, honeycomb- or cartwheel-like growth pattern
- Fascicles spreading between collagen bundles and along septae of subcutaneous fat tissue with entrapment of fat lobules, resulting in a sieve-like appearance
- Mitoses are rare, but number may be increased, when transformation to sarcomatous growth occurs
- Variants include sclerosing, giant cell, myxoid, granular cell and fibrosarcomatous forms
- The pigmented Bednar tumor is a DFSP variant which is rich in melanocytes

Dermatofibrosarcoma Protuberans, Storiform Pattern

Storiform pattern



CD34

Immunohistochemistry: diffusely positive for CD34. Specific translocation t(17;22) and fusion gene may be shown by FISH or RT-PCR respectively.

DD: Keloid; dermatofibroma (usually factor XIIIa positive and CD34 negative).

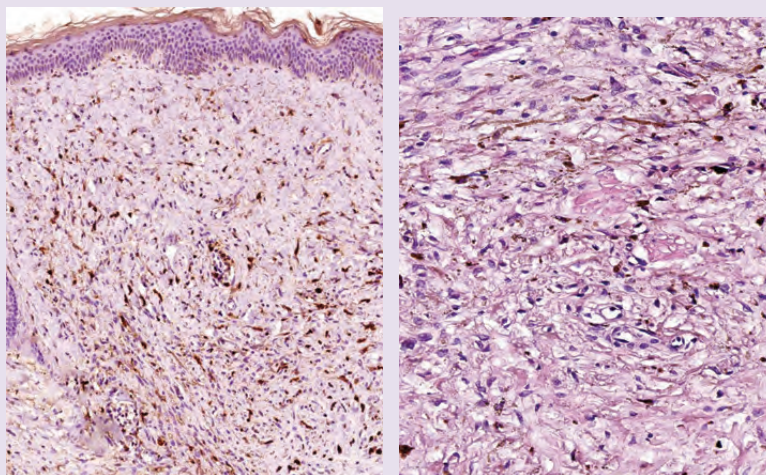
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Variant: Pigmented Dermatofibrosarcoma Protuberans (Bednar's Tumor)

Interspersed pigmented dendritic melanocytes



Cl: Clinical features are the same as found in dermatofibrosarcoma protuberans.

Hi:

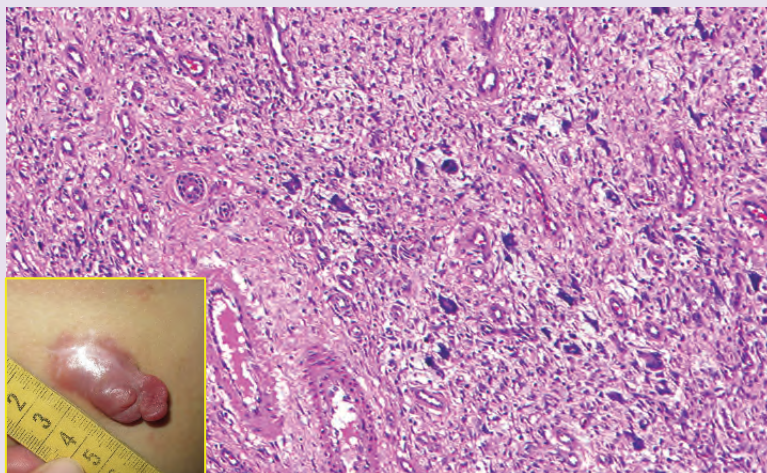
- Typical features of dermatofibrosarcoma protuberans
- Diffuse splaying of intratumoral solitary melanocytes (Melan A positive)

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Variant: Giant Cell Fibroblastoma

Fibrous stroma with stellate and dendritic giant cells. Nodular lesion on the trunk (inset)



Cl: Rare variant of dermatofibrosarcoma protuberans occurring on the chest wall, back, and thigh of children as a poorly circumscribed tumor.

Hi:

- Dermatofibrosarcomatous structures
- Multinuclear stellate or dendritic CD34-positive giant cells
- Myxoid pseudovascular pseudocysts

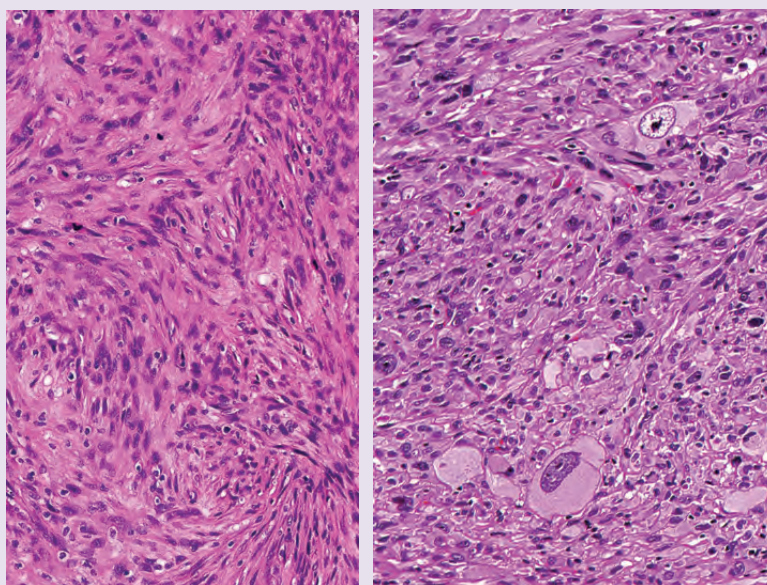
Reference

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Pleomorphic Dermal Sarcoma (PDS)

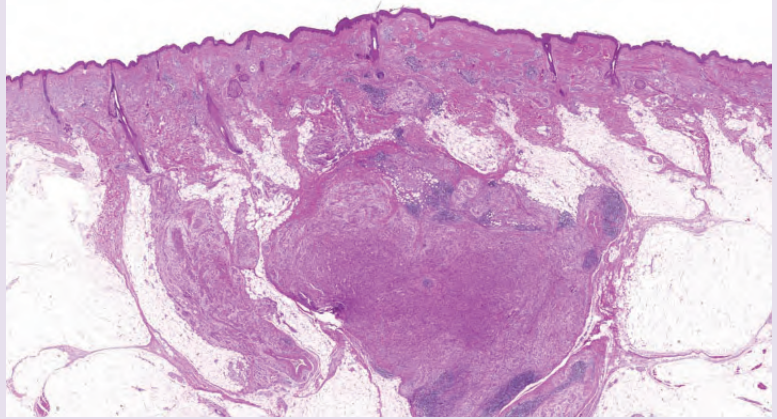
Storiform growth pattern with marked pleomorphism and hyperchromasia (left)

Large atypical cells (right)

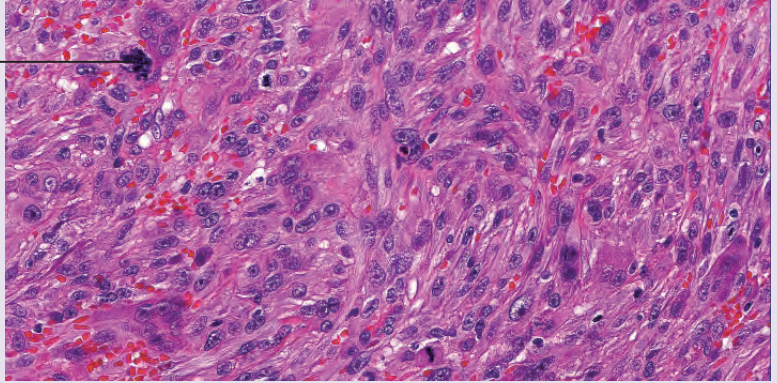


Pleomorphic Dermal Sarcoma (PDS)

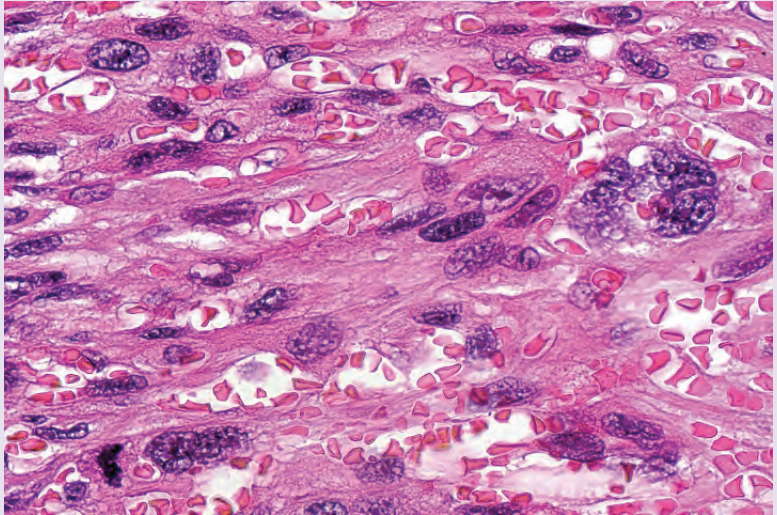
Subcutaneous tumor



Atypical mitosis



Pleomorphic hyperchromatic cells (mid and bottom)



The term “malignant fibrous histiocytoma” (MFH) is outdated and was used to designate a heterogeneous group of sarcomas with markedly anaplastic or pleomorphic features. This obsolete term has been replaced by atypical fibroxanthoma (AFX) for the nodular exophytic form and pleomorphic dermal sarcoma (PDS) for the infiltrative deep variant. Advances in immunohistochemistry and molecular pathology have made it possible to diagnose most of the tumors formerly subsumed under the waste-basket diagnosis of MFH with greater precision.

Cl: The superficial form of “MFH” (AFX) is a nodular, locally aggressive tumor in sun-exposed areas of adults, preferentially in the head and neck, or dorsa of the hands. In the deeper form of “MFH” (PDS), the skin is affected usually as a part of deep involvement of a more aggressive soft tissue tumor, arising most probably from vessels or perivascular myoid cells. Ulceration and necroses are common features in both.

Hi:

- Growth pattern:
 - AFX: strictly symmetrical, exophytic, and superficial, not infiltrative
 - PDS: infiltrative growth with poorly defined margins, reaching the subcutaneous fat
- The common denominators of AFX and PDS are:
 - Spindle-shaped cells, sometimes in storiform pattern
 - Admixture of large, pleomorphic cells with nuclear atypia
 - Variable number of foam cells and giant cells
 - Mitotic activity and necrosis
- Inflammatory, myxoid, angiomatoid, clear cell, pigmented, granular and non-pleomorphic, keloidal, and sclerotic variants have been reported

DD: Spindle cell carcinoma (keratin markers); amelanotic malignant melanoma (melanoma markers).

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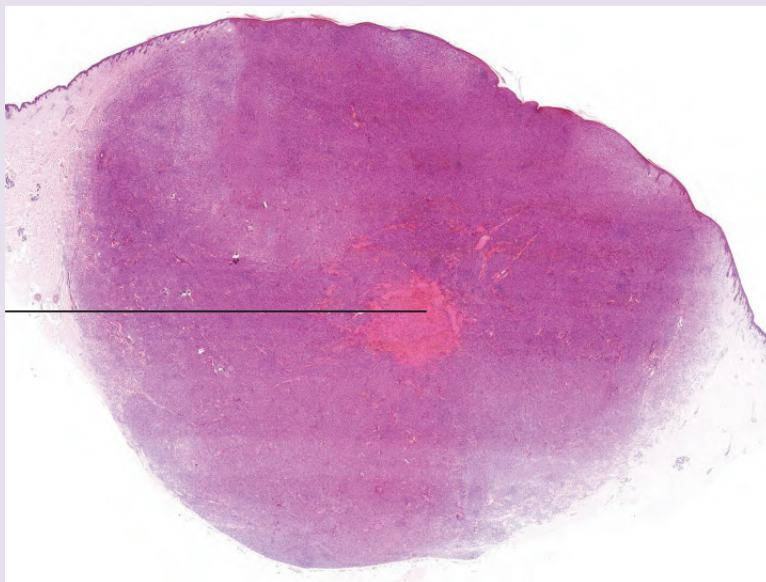
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Miscellaneous Tumors

Epithelioid Sarcoma

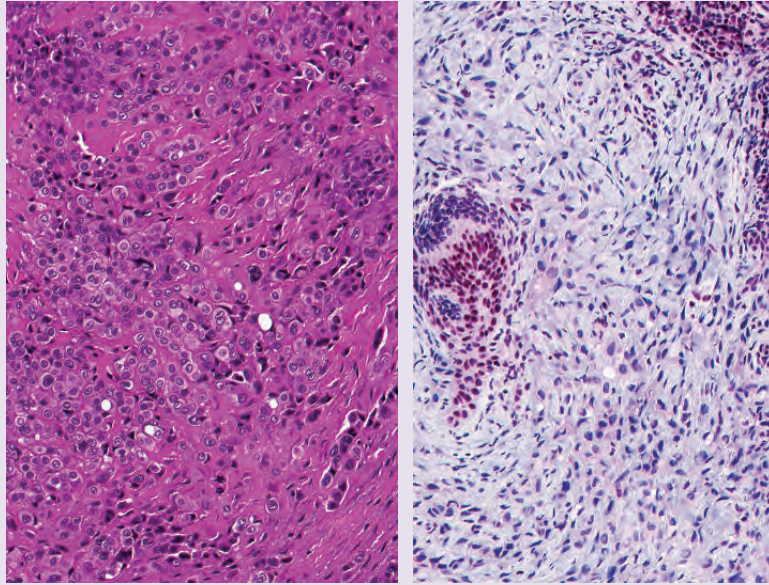
Central necrosis



Epithelioid Sarcoma

Polygonal cells with abundant eosinophilic cytoplasm (left)

Tumor cells are INI1 negative (right)



Cl: Subcutaneous, slowly growing malignant tumor preferentially on the distal extremities of young adults (distal type of epithelioid sarcoma) or at the pelvis and shoulder girdle (proximal type of epithelioid angiosarcoma). Ulceration may occur. Tendency to early multifocal spread and to local recurrences after incomplete excision.

Hi:

- Superficial biopsy may show pseudogranulomatous inflammation, imitating granuloma annulare
- The tumor presents as a poorly defined nodule in the deep dermis, extending into the fat, occasionally multifocal
- Plexiform and diffuse infiltrative growth pattern along the fascia and tendons
- Central necrosis, surrounded by tumor cells in palisade arrangement ("geographical necrosis"), simulating a deep granulomatous process with central necrobiosis
- Polygonal spindle cells with abundant eosinophilic cytoplasm and nuclear atypia

Immunohistochemistry: Tumor cells are positive for vimentin, keratin-markers, EMA, and CD34 while macrophage markers are negative. Tumor suppressor gene *INI1* (*SMARCB1*)

shows conspicuous lack of nuclear expression. INI1 negativity is taken as a hallmark of epithelioid sarcoma.

DD: Deep granuloma annulare; necrobiosis lipoidica; rheumatoid nodule; granulomatous infection; giant cell tumor of tendon sheath; epithelioid angiosarcoma; epithelioid hemangioendothelioma.

References

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Orrock, J.M., Abbott, J.J., Gibson, L.E., and Folpe, A.L. (2009) INI1 and GLUT-1 expression in epithelioid sarcoma and its cutaneous neoplastic and nonneoplastic mimics. *Am J Dermatopathol* **31**(2): 152–6.

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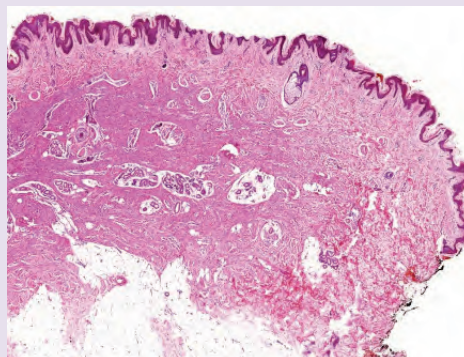
sarcoma-like (pseudomyogenic) hemangioendothelioma, clinically mimicking dermatofibroma, diagnosed by skin biopsy in a 30-year-old man. *J Cutan Pathol* **40**(10): 909–13.

Dermatomyofibroma

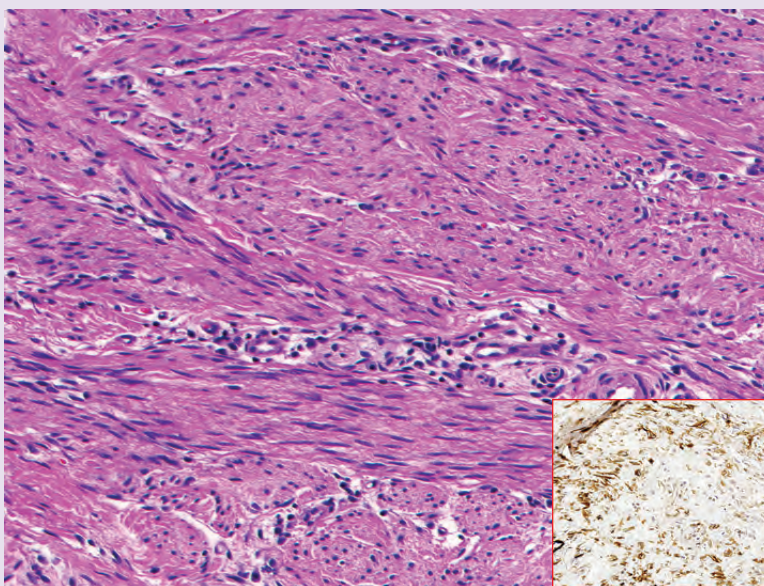
Tumorous plaque on the abdomen



Dermal tumor of horizontally arranged myofibroblasts. Adnexal structures are preserved (right)



Slender fascicles of spindled myofibroblasts



Inset: partial expression of smooth muscle actin (ASMA)

Cl: Benign, plaque-like tumor in young adults and adolescents. Predilection sites are the major skinfolds. Lesions clinically imitate flat dermatofibroma or neurofibroma. The tumor is considered to be an acquired benign myofibroblastic proliferation.

Hi:

- Flat, poorly circumscribed spindle cell proliferation involving the entire dermis
- Horizontally arranged intermingling fascicles of spindled myofibroblasts
- Adnexal structures and elastic fibers are preserved
- No polymorphism or mitotic activity

Immunohistochemistry: Incipient lesions show myofibroblastic expression of alpha smooth

muscle actin (ASMA) while advanced lesions are both ASMA and desmin negative.

DD: Piloleiomyoma; dermatofibroma; fibroblastic connective tissue nevus.

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CHAPTER 6

Vessels

CHAPTER MENU

Hamartomas, Nevi, and Malformations	Hyperplasias
Phacomatosis Pigmentovascularis	Granuloma Pyogenicum (Lobular Capillary Hemangioma; Botryomykoma)
Eccrine Angiomatous Hamartoma	Differential Diagnosis: Pyogenic Granuloma-Like Granulation Tissue
Nevus Anemicus	Bacillary Angiomatosis
Capillary Malformations	Verruga Peruana
Nevus Flammeus (Port-Wine Stain)	Intravascular Papillary Endothelial Hyperplasia (Masson)
Nevus Araneus (Spider Angioma)	Acroangiodermatitis Mali (Pseudo-Kaposi's Sarcoma)
Cutis Marmorata Telangiectatica (van Lohuizen) (Nevus Vascularis Reticularis)	Benign Vascular Neoplasms
Congenital Telangiectatic Erythema (Bloom's Syndrome)	Epithelioid Hemangioma (Angiolymphoid Hyperplasia with Eosinophilia, ALHE)
Venous Malformations	Endothelial Differentiation
Blue Rubber Bleb Nevus Syndrome (Familial Venous Malformation)	Pericytic Differentiation
Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu)	Glomoid and Myoid Differentiation
Angioma Serpiginosum	Recently Described Benign Vascular Tumors
Venular Aneurysm (Venous Lake)	Vascular Neoplasms of Intermediate Malignant Potential
Cavernous Hemangioma (in Maffucci Syndrome)	Kaposi's Sarcoma (KS)
Sinusoidal Hemangioma	Retiform Hemangioendothelioma
Spindle Cell Hemangioma (Formerly Spindle Cell Hemangioendothelioma)	Composite Hemangioendothelioma
Arteriovenous Malformations	Papillary Intralymphatic
Acral Arteriovenous Hemangioma (Cirroid Aneurysm)	Angioendothelioma (PILA)
Glomuvenular Malformation ("Glomangioma")	(Malignant Endovascular Papillary
Lymphatic Malformations	Angioendothelioma (Dabska Tumor); Endovascular Papillary Hemangioendothelioma)
Superficial Lymphatic Malformation (Superficial Lymphangioma)	Radiation-Induced Atypical Vascular Lesion (AVL) (Benign Lymphangiomatous Papule (BLAP))
Cystic Lymphatic Malformation (Cystic Hygroma)	Vascular Neoplasms with High Malignant Potential
Targetoid Hemosiderotic (Hobnail) Hemangioma	Cutaneous Angiosarcoma
Progressive Lymphangioma (Benign Lymphangioendothelioma)	Radiation-Induced (Postradiation) Angiosarcoma
Lymphangiomatosis	Epithelioid Hemangioendothelioma
Angiokeratomas	Epithelioid Angiosarcoma
Verrucous Hemangioma (Venous Malformation)	Differential Diagnosis: Acantholytic (Angiosarcoma-Like) Squamous Cell Carcinoma
Variant: Solitary Angiokeratoma	Glomangiosarcoma (Malignant Glomus Tumor)
Variant: Angiokeratoma Circumscriptum Naeviformis	Other Neoplasms with Significant Vascular Component
Variant: Fordyce Angiokeratoma	Multinucleate Angiohistiocyte
Variant: Angiokeratoma Acroasphycticum Digitorum (Mibelli)	Angiofibroma (Adenoma Sebaceum Associated with Pringle–Bourneville Disease)
Variant: Multiple "Pinpoint" Angiokeratomas (Angiokeratoma Corporis Diffusum; Fabry's Disease)	Angiolipoma
Variant: Acral Pseudolymphomatous Angiokeratoma of Children (APACHE)	Angiolipoleiomyoma (Angiomyolipoma)
	Angiomyxoma
	Intralymphatic Histiocytosis
	Kimura's Disease

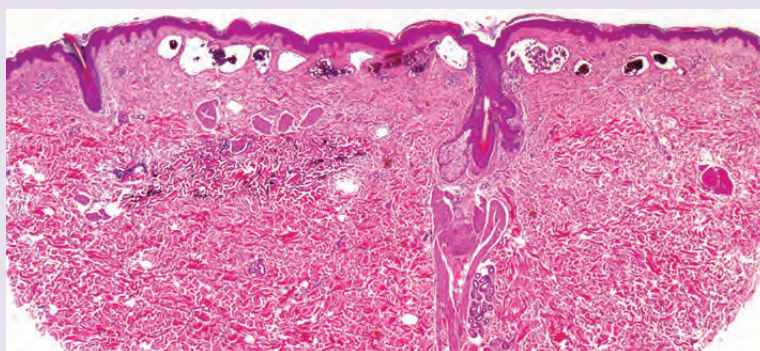
Hamartomas, Nevi, and Malformations

Phacomatosis Pigmentovascularis

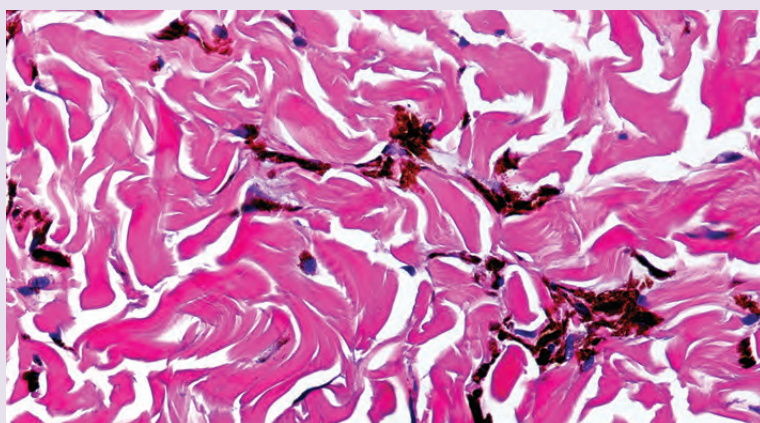
Nevus flammeus (trunk) and nevus pigmentosus (buttocks) in a baby



Dilated capillaries in the papillary dermis



Pigment-loaded dendritic cells in the dermis

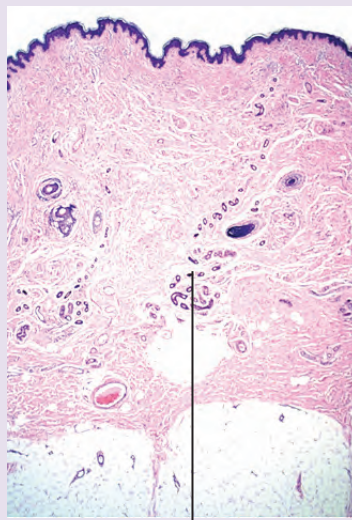


Variants:

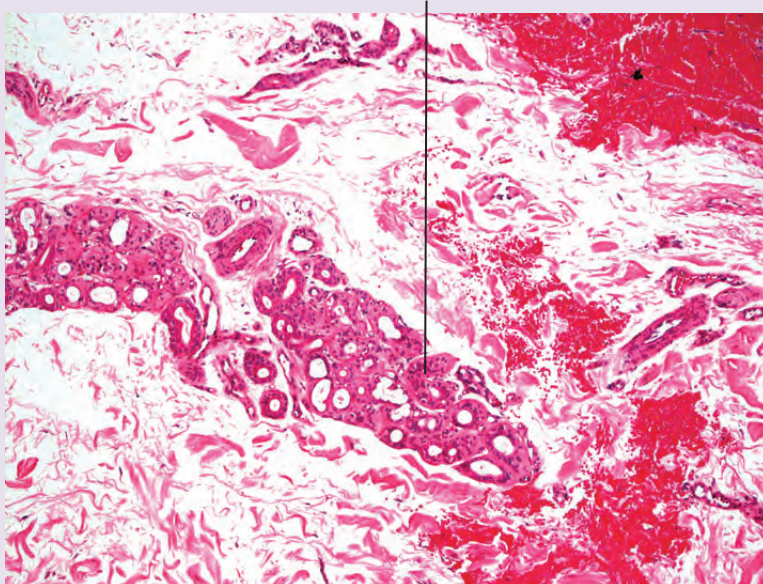
- Type I: Nevus flammeus and nevus pigmentosus verrucosus
- Type II: Nevus flammeus and Mongolian spot (dermal melanocytosis)
- Type III: Nevus flammeus and nevus spilus
- Type IV: Nevus flammeus and nevus spilus and Mongolian spot and/or nevus anemicus

Eccrine Angiomatous Hamartoma

Plantar
angiomatous
plaque (left)



Angiomatous lesion with lobules of sweat glands and ducts



Cl: Red hyperhidrotic plaques, preferentially on palms and soles.

Hi: Increased number of lobularly grouped sweat glands and ducts in close proximity to dilated small blood vessels.

DD: Vascular malformations.

References

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- Requena, L. and Sanguenza, O.P. (1997) Cutaneous vascular anomalies. Part I. Hamartomas, malformations,

and dilation of preexisting vessels. *J Am Acad Dermatol* **37**(4): 523–49; quiz 549–52.

Sanmartin, O., Botella, R., Alegre, V., Martinez, A., and Aliaga, A. (1992) Congenital eccrine angiomatous hamartoma. *Am J Dermatopathol* **14**(2): 161–4.

Nevus Anemicus

This congenital lesion has a functional (vasoconstriction) rather than anatomical (decreased number of capillaries) background. Using reflectance confocal microscopy, there is no difference compared with normal skin. Association with neurofibromatosis type 1 and other syndromes is common.

Cl: Pale macules, especially when surrounding skin is irritated.

Hi: The skin histologically appears normal.

DD (clinical): Vitiligo; nevus depigmentosus.

References

Ahkami, R.N. and Schwartz, R.A. (1999) Nevus anemicus. *Dermatology* **198**(4): 327–9.

Errichetti, E. and Piccirillo, A. (2016) Co-occurrence of nevus anemicus and Becker nevus: a possible instance of pseudodidymosis? *Int J Dermatol* **55**(4): e219–20.

Lai, L.G. and Xu, A.E. (2011) In vivo reflectance confocal microscopy imaging of vitiligo, nevus depigmentosus and nevus anemicus. *Skin Res Technol* **17**(4): 404–10.

Ma, H., Liao, M., Qiu, S., Luo, R., Lu, R., and Lu, C. (2015) The case of a boy with nevus of Ota, extensive Mongolian spot, nevus flammeus, nevus anemicus and cutis marmorata telangiectatica congenita: a unique instance of phacomatosis pigmentovascularis. *An Bras Dermatol* **90**(3 Suppl 1): 10–12.

Mizutani, H., Ohyanagi, S., Umeda, Y., Shimizu, M., and Kupper, T.S. (1997) Loss of cutaneous delayed hypersensitivity reactions in nevus anemicus. Evidence for close concordance of cutaneous delayed hypersensitivity and endothelial E-selectin expression. *Arch Dermatol* **133**(5): 617–20.

Sachs, C. and Lipsker, D. (2016) Nevus anemicus and Bier spots in tuberous sclerosis complex. *JAMA Dermatol* **152**(2): 217–18.

Salvini, C., Fabroni, C., Francalanci, S., Massi, D., and Difonzo, E.M. (2007) Generalized nevus anaemicus in an adult. *J Eur Acad Dermatol Venereol* **21**(8): 1142–4.

Vaassen, P. and Rosenbaum, T. (2016) Nevus anemicus as an additional diagnostic marker of neurofibromatosis type 1 in childhood. *Neuropediatrics* **47**(3): 190–3.

Capillary Malformations

Nevus Flammeus (Port-Wine Stain)

Nevus flammeus

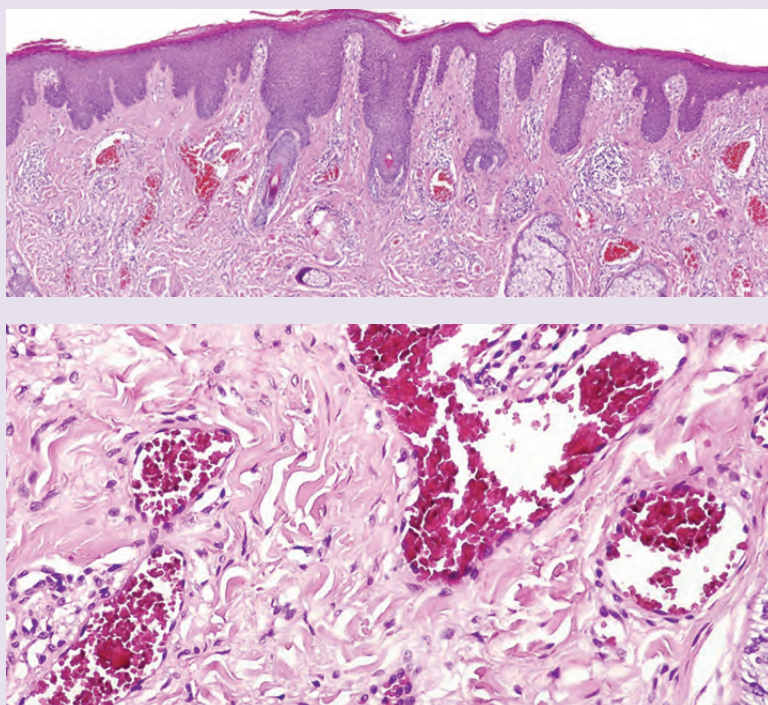


Cl: Congenital pink or red-wine colored patch, which proportionally enlarges with body growth. No regression. Nodular or plaque-like hypertrophy in higher age. Association with several syndromes: Sturge–Weber (congenital, but not

familial angiomatosis affecting the skin of the face, leptomeninges, and brain), Klippel–Trénaunay (nevus flammeus, congenital AV fistulae and hypertrophy of the bones and soft tissues in affected area).

Nevus Flammeus (Port-Wine Stain)

Cavernous dilatation of postcapillary venules (mid and bottom)



Hi: In early lesions, the histological picture is often inconspicuous and difficult to evaluate.

- Slightly increased number and dilation of postcapillary venules of the upper vascular plexus
- Later, variably dilated blood vessels appear
- In adults, there are usually many cavernous vascular spaces, vascular proliferations, and fibrosis

Immunohistochemistry: Distinct endothelial negativity for WT1 (immunohistochemical hallmark of malformative endothelia).

References

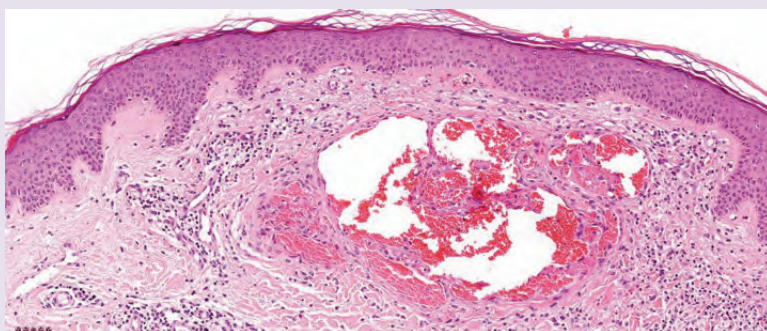
- Finley, J.L., Noe, J.M., Arndt, K.A., and Rosen, S. (1984) Port-wine stains. Morphologic variations and developmental lesions. *Arch Dermatol* **120**(11): 1453–5.
- Holloway, K.B., Ramos-Caro, F.A., Brownlee, R.E. Jr, and Flowers, F.P. (1994) Giant proliferative hemangiomas arising in a port-wine stain. *J Am Acad Dermatol* **31**(4): 675–6.
- Rosen, S. and Smoller, B.R. (1987) Port-wine stains: a new hypothesis. *J Am Acad Dermatol* **17**(1): 164–6.

Nevus Araneus (Spider Angioma)

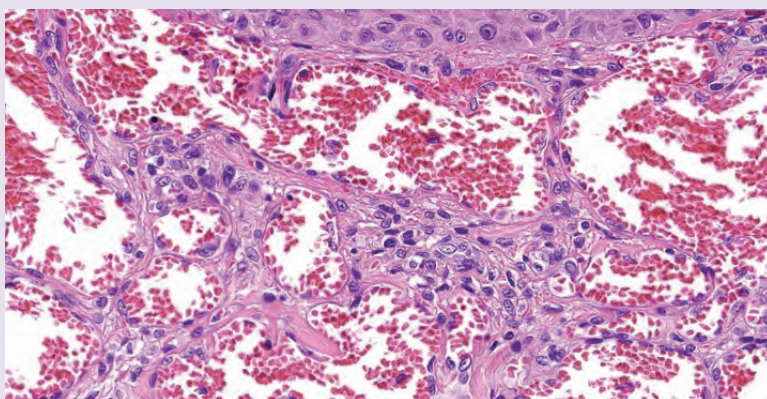
Central angioma
with radial
spreading
capillaries



Dilated vascular
spaces with
thrombi. Dilatation
of vessels in the
periphery



Dilated vascular
spaces



Cl: Tiny angiomatous lesion, pulsating, blanching, and refilling under diascopy. Array of tiny capillaries spread in the periphery of the lesion in a spider web fashion. Spontaneous spider angiomas are seen on the face of young individuals. Multiple symptomatic spider angiomas occur in systemic sclerosis, pregnancy, and hepatic cirrhosis.

Hi:

- In serial sections: central arteriole in the superficial dermis
- Small anastomosing venules in the periphery

DD: Telangiectases.

Reference

Bean, W.B. (1958) *Vascular Spider and Related Lesions of the Skin*. Springfield: Thomas.

Cutis Marmorata Telangiectatica (van Lohuizen) (Nevus Vascularis Reticularis)

Blue-red vascular mottling of the skin in a child

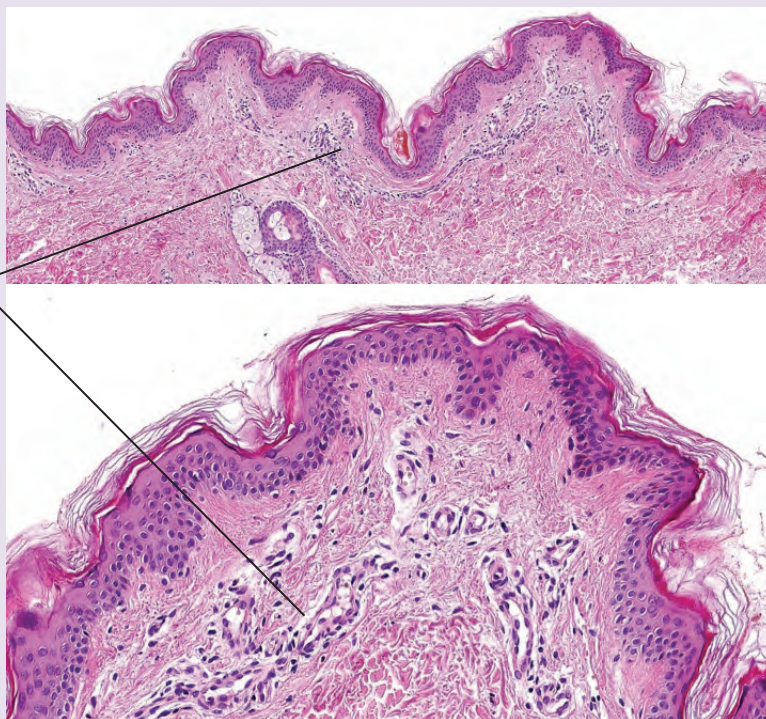


Cl: Congenital reticular or netlike vascular mottling of the skin, simulating livedo reticularis or racemosa and spreading mostly unilaterally over

a large area of extremities or trunk. Superficial ulceration can occur in rare cases. Improvement of the condition with age.

Cutis Marmorata Telangiectatica (van Lohuizen) (Nevus Vascularis Reticularis)

Slight increase and dilatation of small blood vessels in the upper dermis



Hi: Inconspicuous areas with increased and dilated thin-walled blood vessels. The histology is usually not diagnostic and clinical correlation is required. However, hemangiomatous histological features may be seen.

DD: Functional cutis marmorata; livedo reticularis; vascular malformations; lupus erythematosus.

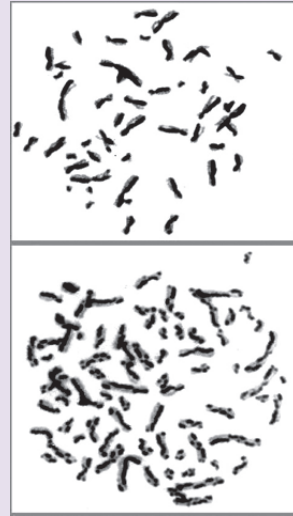
Reference

Fujita, M., Darmstadt, G.L., and Dinulos, J.G. (2003) Cutis marmorata telangiectatica congenita with hemangiomatous histopathologic features. *J Am Acad Dermatol* **48**(6): 950–4.

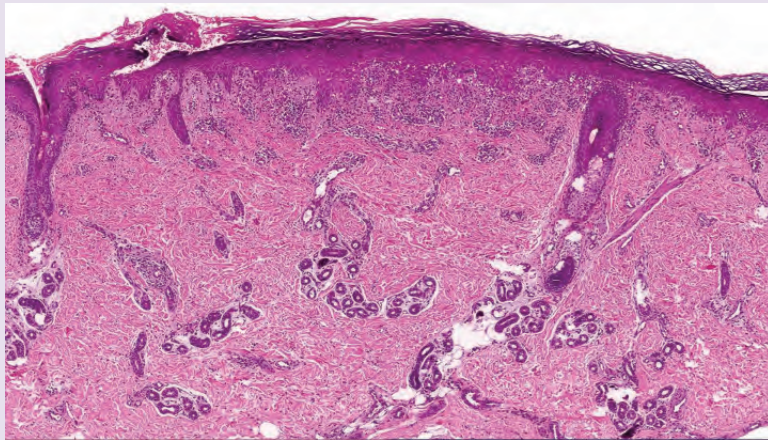
Congenital Telangiectatic Erythema (Bloom's Syndrome)

Telangiectatic erythema of the cheeks in a young boy

Various degrees of sister chromatid exchanges (BrdU-labelling) in a disease-free proband (above) and in a proband with Bloom syndrome (below)



Acanthosis, papillomatosis, lichenoid lymphocytic infiltrate and telangiectasias



Diagnosis has to be confirmed by demonstration of increased sister chromatid exchange.

Cl: Inherited disease showing essential telangiectasia of the cheeks and photosensitivity, which lead to lupus erythematosus or lichen planus-like symptoms and finally result in a poikilodermatous picture. Growth retardation, triangular face; hypo- and hyperpigmentations. Patients are prone to develop malignancies and have a reduced life expectancy.

Hi:

- Acanthosis, papillomatosis, hypergranulosis, and elongation of rete ridges
- Dense epidermotropic lymphocytic infiltrate in the upper dermis, simulating lichen planus or cutaneous T-cell lymphoma
- Increased number and dilation of small blood vessels in the upper dermis resulting in telangiectatic erythema

DD: Syndromes with poikiloderma; lupus erythematosus; lichen planus; cutaneous T-cell lymphoma (see pseudo-mycosis fungoides); telangiectatic erythemas.

References

Bloom, D. (1954) Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs; probably a syndrome entity. *AMA Am J Dis Child* **88**(6): 754–8.

Grob, M., Wyss, M., Spycher, M.A., et al. (1998) Histopathologic and ultrastructural study of lupus-like skin lesions in a patient with Bloom syndrome. *J Cutan Pathol* **25**(5): 275–8.

McGowan, J., Maize, J., and Cook, J. (2009) Lupus-like histopathology in bloom syndrome: reexamining the clinical and histologic implications of photosensitivity. *Am J Dermatopathol* **31**(8): 786–91.

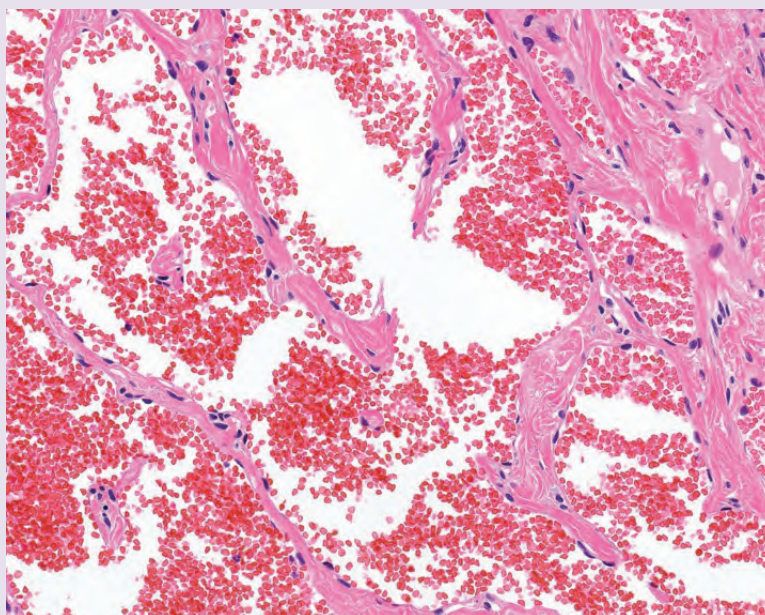
Venous Malformations

Blue Rubber Bleb Nevus Syndrome (Familial Venous Malformation)

Soft blue cutaneous and subcutaneous nodules



Dilated capillary spaces



Cl: Autosomal dominant venous malformations. Variant of cavernous malformation (“venous hemangioma”) accompanied by similar lesions in the gastrointestinal tract and in other visceral organs. Sometimes accompanied by hyperhidrosis.

Hi:

- Deep dermis and subcutis

- Dilated thin-walled vascular channels with WT1-negative endothelia

- Thickened vessel walls with caliber variation

DD: Lymphatic and glomuvenous malformations (glomangioma); portwine stain; arteriovenous malformations; juvenile capillary hemangioma.

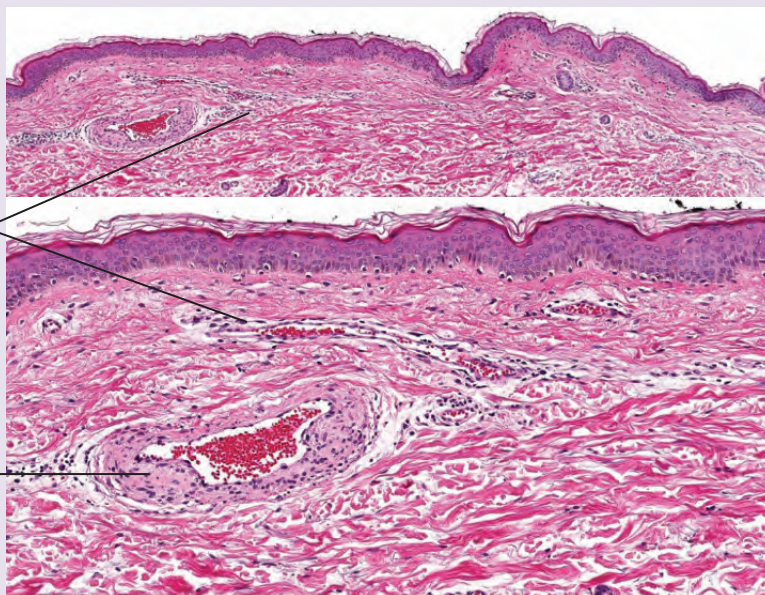
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu)

Telangiectatic angiomas: ear, lips, tongue, paronychium



Thin walled ectatic capillaries

Malformative vein



CI: Rare autosomal dominant disorder with small mucocutaneous telangiectatic angiomias and arteriovenous fistulae, especially on the lips, nose, ears, and large visceral organs, which tend to bleed, causing anemia.

Hi:

- Dilated thin-walled ectatic venules in the upper dermis

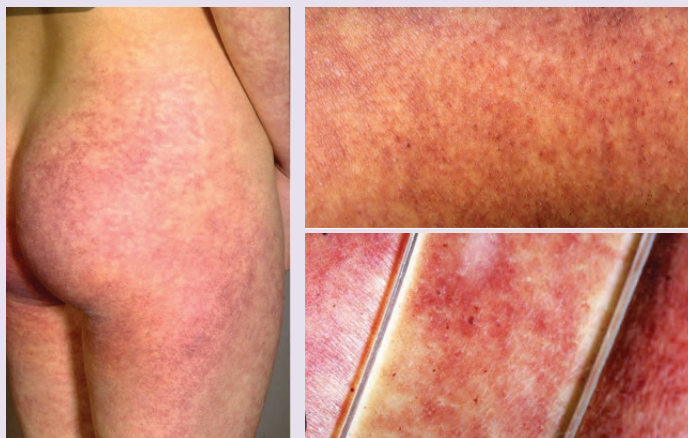
- Aberrant, thick-walled arteries in the deeper dermis

DD: Multiple spider nevi; multiple cherry angiomias; diseases associated with multiple angiokeratomas.

Angioma Serpiginosum

Dot-like ectatic capillaries

Little bleaching under diaphanoscopy (right bottom)

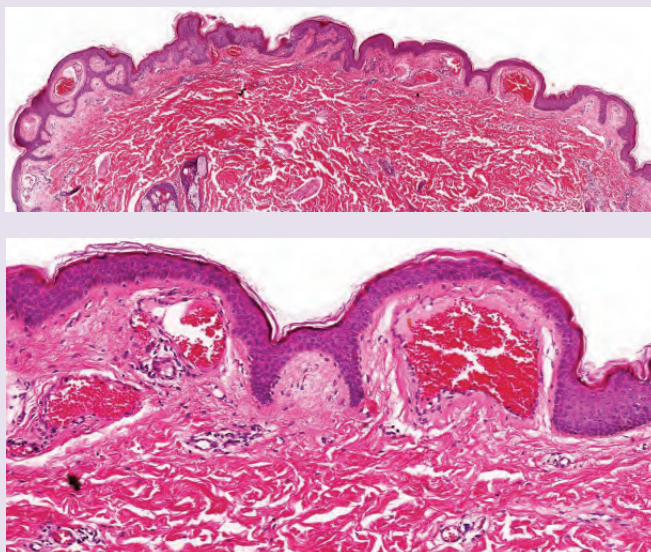


CI: This microvenular malformation starts early in childhood and affects almost exclusively girls; some cases are familial. The buttocks, thighs or arms are the preferential localisation for grouped,

dot-like ectatic capillaries. Peripheral growth and central regression result in a serpiginous pattern. There may be a Blaschko line distribution.

Angioma Serpiginosum

Dilated and blood-filled venules in the papillary dermis



Hi: Dilated small vessels in the papillary dermis.

DD: Purpura; hereditary hemorrhagic telangiectasia; multiple angiokeratomas.

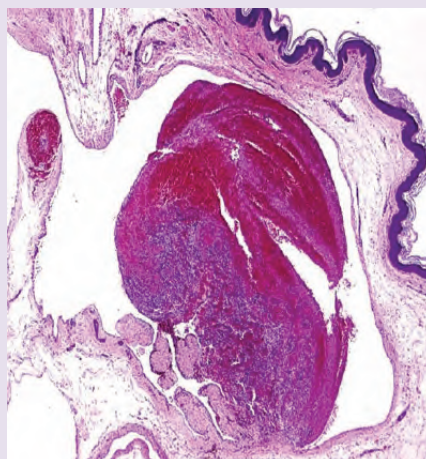
References

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- Chen, W., Liu, T.J., Yang, Y.C., and Happle, R. (2006) Angioma serpiginosum arranged in a systematized segmental pattern suggesting mosaicism. *Dermatology* **213**(3): 236–8.
- Cox, N.H. and Paterson, W.D. (1991) Angioma serpiginosum: a simulator of purpura. *Postgrad Med J* **67**(794): 1065–6.
- Das, D., Nayak, C.S., and Tambe, S.A. (2016) Blaschko-linear angioma serpiginosum. *Indian J Dermatol Venereol Leprol* **82**(3): 335–7.
- Sancheti, K., Das, A., Podder, I., and Gharami, R.C. (2016) Angioma serpiginosum in a patchy and blaschkoid distribution: a rare condition with an unconventional presentation. *Indian J Dermatol* **61**(5): 570–2.

Venular Aneurysm (Venous Lake)

Multiple blue-black soft papules on the cheek (left)

Thin-walled angiomatous space with thrombus (right)



Cl: Solitary or multiple blue-black soft angiomatous papules, preferentially on the lips, in older people, simulating a melanocytic lesion.

Hi: Large ectatic thin-walled thrombosed vascular space(s) in the upper dermis.

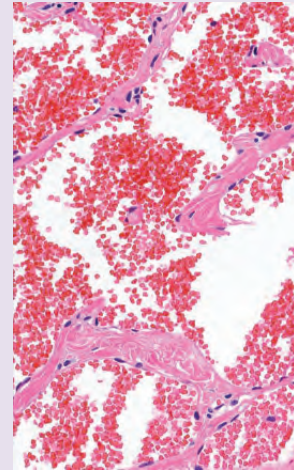
DD: Telangiectases; glomangioma; blue rubber bleb nevus and other venous malformations.

Reference

- Singh, S., Khanna, N., Ramam, M., and Singh, M. (2013) Solitary glomangioma mimicking a venous lake at an unusual site. *Int J Dermatol* **52**(11): 1409–11.

Cavernous Hemangioma (in Maffucci Syndrome)

Large cavernous venous malformation, showing subcutaneous and exophytic growth



Cl: Inherited venous malformation, in which large and deep cavernous hemangiomas are associated with dyschondroplasia of the hands and feet and other symptoms. No spontaneous regression.

Hi: Variety of mostly large, cavernous vascular spaces, lined by endothelium; thrombi, calcifications. Areas corresponding to capillary hemangioma may be found.

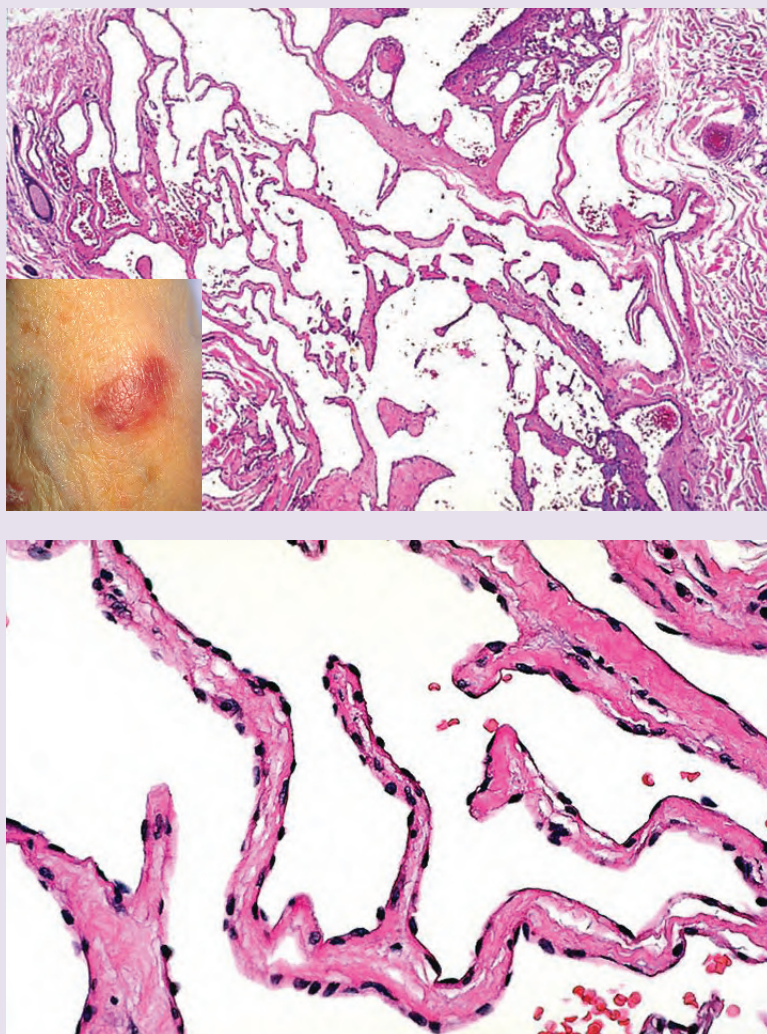
Reference

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Sinusoidal Hemangioma

Bruise-like hemangioma on the arm (inset)

Labyrinthian pattern of anastomosing vascular channels with septa and folds of regular endothelia (top and bottom)



CI: Variant of cavernous venous malformations, presenting as a solitary cutaneous-subcutaneous violaceous nodule. Important differential diagnosis for well-differentiated angiosarcoma of the female breast parenchyma.

Hi:

- Lobular tumor in the deep dermis and subcutis
- Thin-walled anastomosing and interconnected lacunar vascular spaces
- Pseudopapillary projections, septa, and endothelial folds reaching into the lumina

- Malformative venous vessels with WT1-negative endothelia

DD: Well-differentiated angiosarcoma (of the female breast parenchyma).

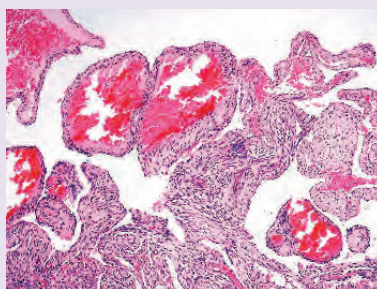
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Spindle Cell Hemangioma (Formerly Spindle Cell Hemangioendothelioma)

Blue-red cutaneous nodule on the planta (left)
Cavernous vascular spaces with thrombi (right)

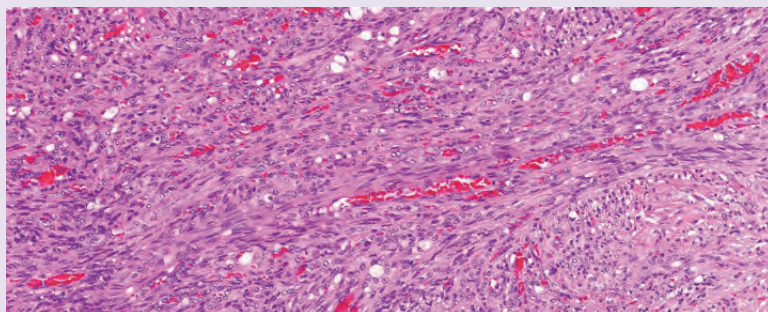


CI: Arteriovenous-lymphatic malformation, presenting as solitary or multiple blue or blue-red, sometimes painful nodules, mostly in adults, preferentially on the extremities. Association with Maffucci syndrome and Klippel–Trenaunay syndrome. Does not metastasize. Reported

pseudo-recurrences (in >50% of excised lesions) are typical persistences of incompletely excised vascular malformations with a multicentric vascular growth pattern, which is highly characteristic of spindle cell hemangioma.

Spindle Cell Hemangioma (Formerly Spindle Cell Hemangioendothelioma)

Fascicles composed of spindle cells (pericytes) and epithelioid endothelial cells with vacuoles (“pseudo-fat cells”)

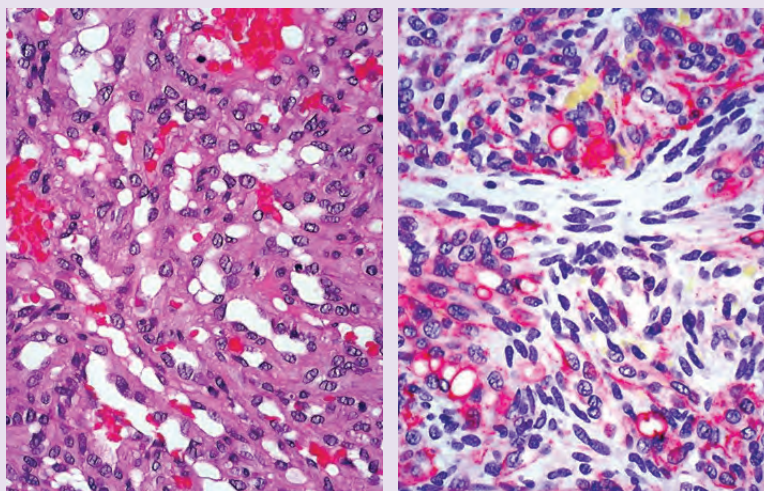


Hi:

- Biphasic vascular tumor composed of solid “kaposiform” zones and richly vascularized cavernous areas
 - Solid cellular (kaposiform) zones contain alpha smooth muscle actin-positive pericytes and CD31-positive endothelia in a compact layered arrangement (“lasagne pattern”). Pericytes are spindle-shaped, while the endothelia are cuboidal or roundish, sometimes with intracytoplasmic vacuoles (“pseudo-fat cells”)
 - Vascular zones are composed of lacuna-like dilated thin-walled venous spaces with thin endothelial septa and folds (“Roman bridges”). There may be thrombi and phleboliths
- Importantly, there are foci of podoplanin positivity as an indicator of the malformative nature of the lesion. Endothelia are negative for HHV8 and MYC
- Accompanying thick-walled malformative vessels are often present

Spindle Cell Hemangioma (Formerly Spindle Cell Hemangioendothelioma)

Epithelioid endothelial cells with vacuoles (left), CD31 + (right)



DD: Kaposi's sarcoma; kaposiform hemangioendothelioma; tufted hemangioma.

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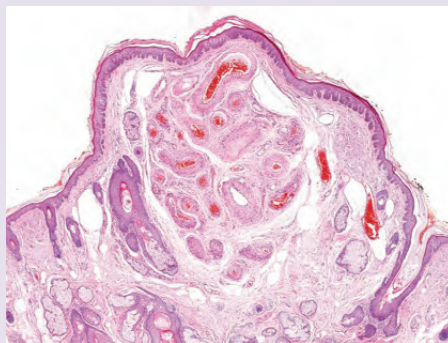
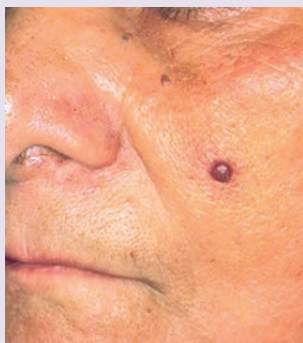
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Arteriovenous Malformations

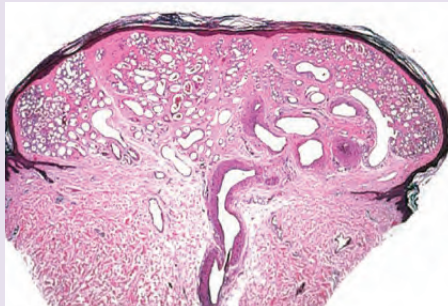
Arteriovenous malformations (arteriovenous hemangioma) are vascular lesions, composed of capillaries, veins, and arteries.

Acral Arteriovenous Hemangioma (Cirroid Aneurysm)

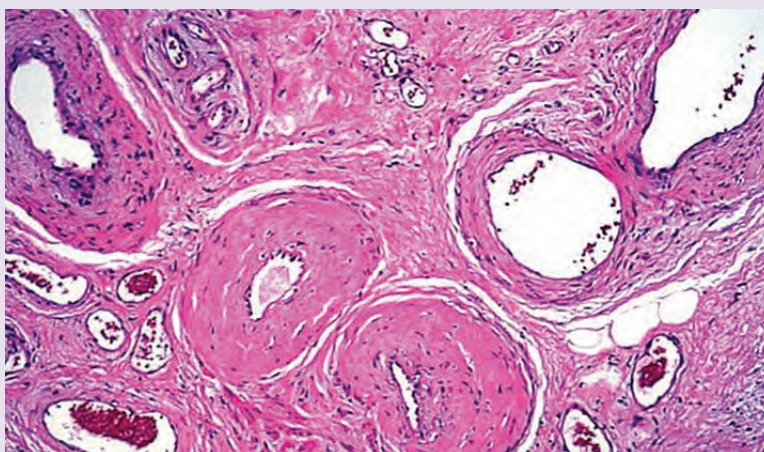
Angiomatous lesions on the cheek (top left) and the temple (mid left)



Exophytic aneurysmatic aggregation of vessels of variable calibers (top and mid right)



Thick-walled vessels juxtaposed to dilated venular spaces



Cl: Solitary red-blue nodule, preferentially in the head and neck area of adults. The nosological classification of cirroid aneurysm (aneurysm, arteriovenous shunt, venous hemangioma, malformation or hamartoma) is still a matter of debate.

Hi:

- Aggregation of small venous or arterial vessels
- Thick fibromuscular vessel walls with elastic fibers
- Lumina show variable diameter with marked caliber variation of all vessels throughout the lesion
- Single layer of endothelial cells
- Fibrous, sometimes myxoid stroma

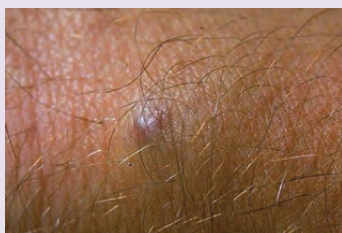
- WT1-positive endothelia (which militates against the malformation hypothesis)

References

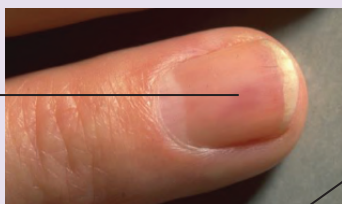
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Glomuvenular Malformation (“Glomangioma”)

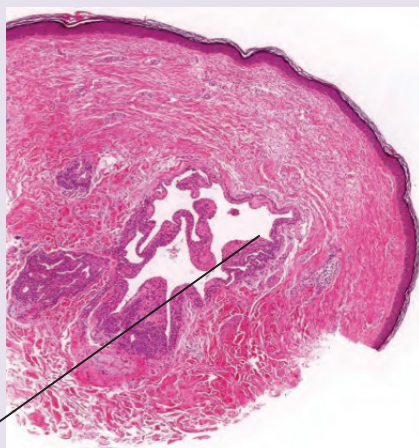
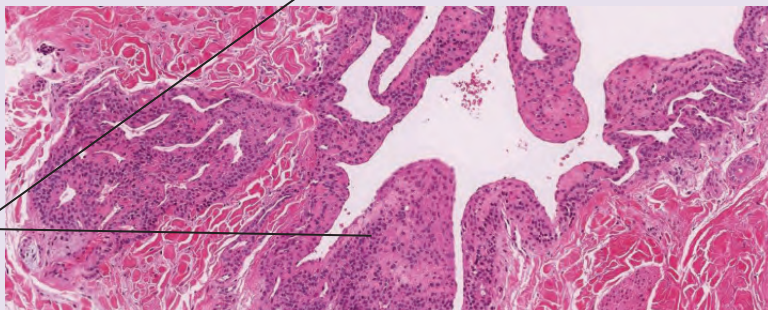
Bluish nodule on the arm



Red subungual lesion

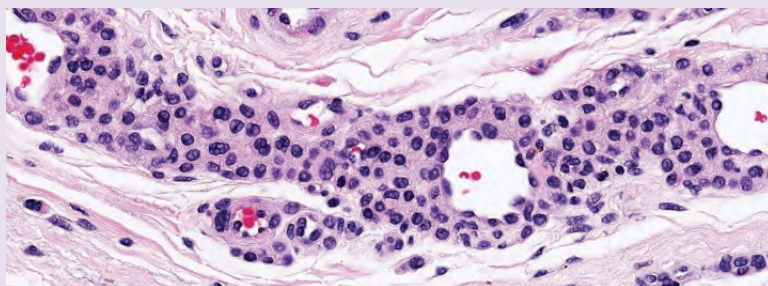


Dilated malformative venous spaces, partially surrounded by glomus cells

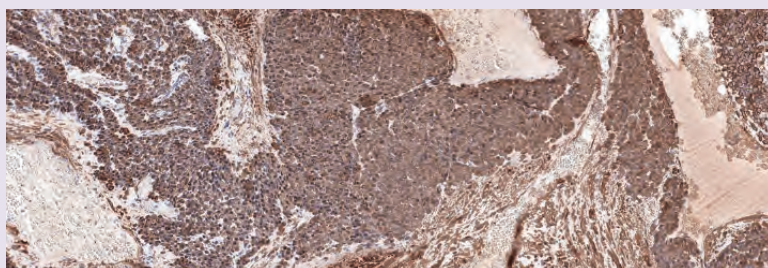


Glomuvenular Malformation ("Glomangioma")

Glomus cells
showing typical
cuboidal shapes



ASMA-positive
glomus cells



Glomus tumor originates from modified smooth muscle cells of the outer vascular wall while glomuvenular malformation ("glomangioma") represents a classic venular vascular malformation with focal masses of glomus cells in the outer vessel wall. The common denominator of both entities is the glomus cell, a small cuboid myoid cell that is characteristically enveloped by a collagen IV-positive outer sheath.

Cl: Glomuvenular malformation presents as blue-violet nodules, painful spontaneously or upon pressure, as in glomus tumor. Large anastomosing venular malformative vessels in deeper layers of the skin and subcutis are the characteristic feature.

Hi:

- Histopathologically, the glomus cell proliferations are divided into three morphological subtypes:
 - Glomuvenular malformation ("glomangioma"), showing large dilated venules and veins with WT1-negative endothelia and broad rims of aggregated glomus cells in the outer vessel wall
 - Solid glomus tumor is composed of densely packed sheets of isomorphic cuboid glomus cells, with minimal accompanying vascularization

- Glomangiomyoma is a morphological variant which contains glomus cells of various shapes; usually, there is a gradual blending of sheets of conventional glomus cells into areas with glomoid spindle cell variation
- Immunophenotypically, glomus cells express alpha smooth muscle actin and are individually enveloped by collagen IV-positive fibers. Myxoid variants express CD34
- Plaque-like telangiectatic lesions are rare. They are variants of the glomuvenular malformation

DD: Blue rubber bleb nevus syndrome; cavernous hemangioma; blue nevus; melanoma; nodular hidradenoma.

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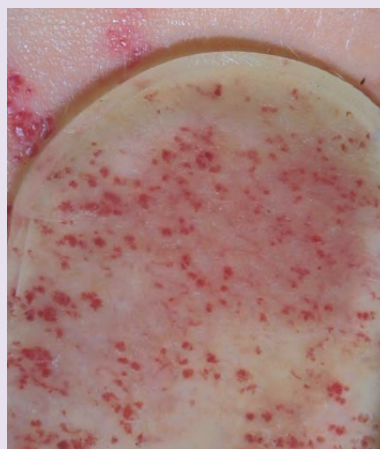
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Lymphatic Malformations

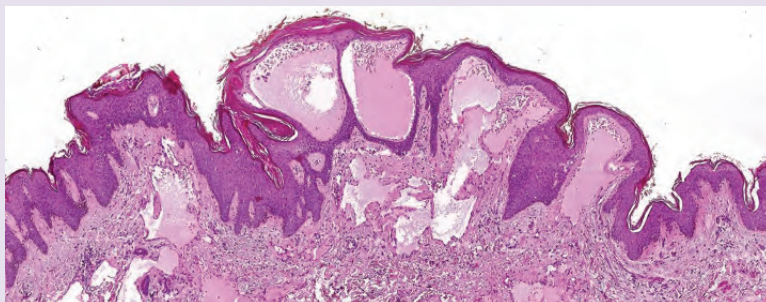
Superficial Lymphatic Malformation (Superficial Lymphangioma)

Aggregates of small cystic papules (left)

Diascopy (right)



Subepidermal malformative lymphatic vessels



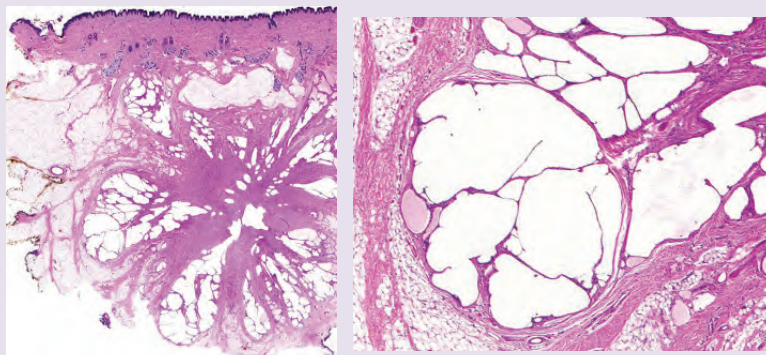
In the past, vascular lesions with a lymphatic vessel wall were uniformly classified as lymphangiomas. This classification has changed dramatically with the advent of new diagnostic imaging techniques and immunohistochemical methods. Presently, there is a tendency to subsume all lymphatic vascular growths under the heading of lymphatic vascular malformations.

- Superficial lymphatic malformations (lymphangioma; lymphangioma circumscriptum cysticum)

- Deep lymphatic malformations (lymphangioma; cavernous lymphangioma; cystic hygroma)
- Lymphangiomatosis – as a specific malformative variant with diffuse involvement of large body planes
- Clinical variants of superficial lymphatic malformations: targetoid hemosiderotic hemangioma (hobnail hemangioma); progressive lymphangioma (benign lymphangioendothelioma)

Cystic Lymphatic Malformation (Cystic Hygroma)

Cavernous lymphatic spaces



CI:

- *Superficial types*: mostly grouped or aggregated red or clear small vesicular papules (“frog spawn”) on the extremities, tongue or mucous membranes. The surface may be verrucous. Some lesions may be hemorrhagic (“hematolymphangioma”)
- *Deep types*: soft skin-colored indurations and swellings
- *Lymphangiomatosis*: diffuse swelling of a limb; later stages show dark brownish skin

Hi:

- In the upper dermis: dilated thin-walled lymphatic vessels, some containing erythrocytes. No myoid/pericytic vessel wall. Accompanying hemosiderosis
- Deeper forms show lymphatic vessels with myoid vessel walls. Remarkably, there are caliber variations within the same malformative vessel (“thin-thick vessel wall”)
- Common denominators are endothelial WT1 negativity (indicator of malformative endothelium) and expression of podoplanin

DD: Secondary lymphangiectases following surgery or radiation therapy; angiokeratoma; verrucous hemangioma; herpes virus infections; Kaposi’s sarcoma.

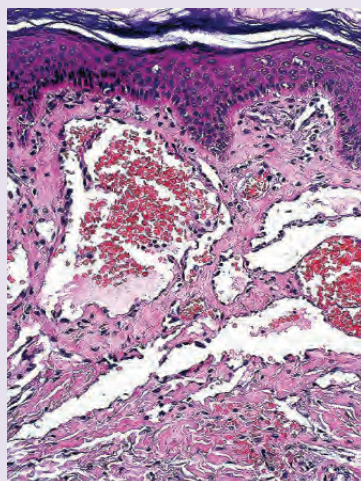
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Targetoid Hemosiderotic (Hobnail) Hemangioma

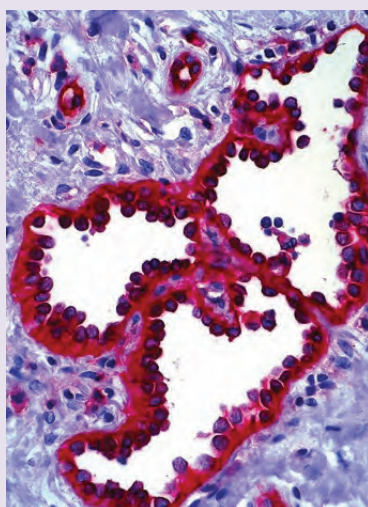
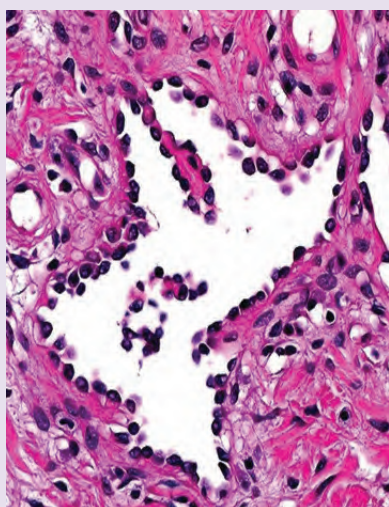
Targetoid pigmented lesion (left)

Superficial part showing dilated lymphatic vessels (right)



Dilated vessel with protrusions of isomorphic "lymphocyte-like" lymphatic endothelial cells ("hobnails") (left);

CD31-positive endothelia (right)



CI: Solitary superficial lymphatic vascular malformation. Flat angiomatous patch, often of targetoid appearance: rusty colored papule in the middle, surrounded by paler erythematous ring and by darker area with ecchymoses in the periphery. Lesions characteristically imitate pigmented nevi.

Hi: Hobnail hemangioma presents with a characteristic zonation pattern.

- **Upper dermis:** dilated bizarre vessels with plump, isomorphic ("lymphocyte-like") endothelia ("hobnails") protruding into the lumina

- **Deep dermis:** collapsed lymphatic vessels with very narrow lumina amidst a fibrous stroma containing many siderophages

Immunohistochemistry: Endothelial cells express the lymphatic marker podoplanin and are negative for WT1. An outer myoid vessel wall (alpha smooth muscle actin) does not exist.

DD: Kaposi's sarcoma; benign (progressive) lymphangioendothelioma; melanocytic nevus.

References

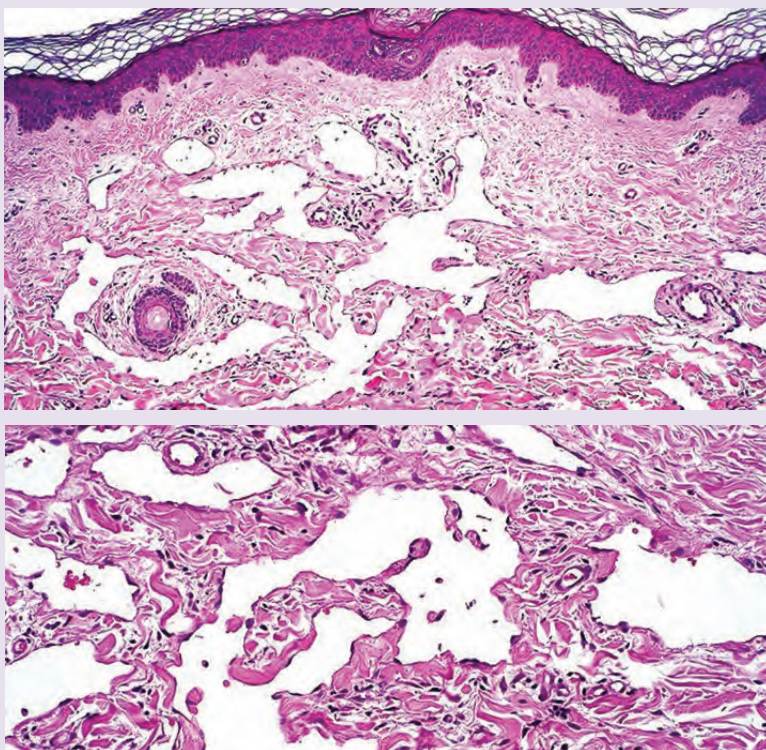
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Progressive Lymphangioma (Benign Lymphangioendothelioma)

Typical brownish centrifugally progressing plaque



Bizarre anastomizing dilated thin walled lymphatic vessels with regular endothelia



Cl: Rare single, brown, slowly expanding macular lymphatic malformation, resembling a large lentigo or even evolving early Kaposi's sarcoma.

Hi: Dilated superficial thin-walled bizarrely anastomosing lymphatic spaces spreading between collagen bundles. The lack of cellular atypia allows for differentiation from angiosarcoma. Endothelial cells are negative for HHV8 (DD: Kaposi's sarcoma) and MYC, Ki67 (DD: angiosarcoma).

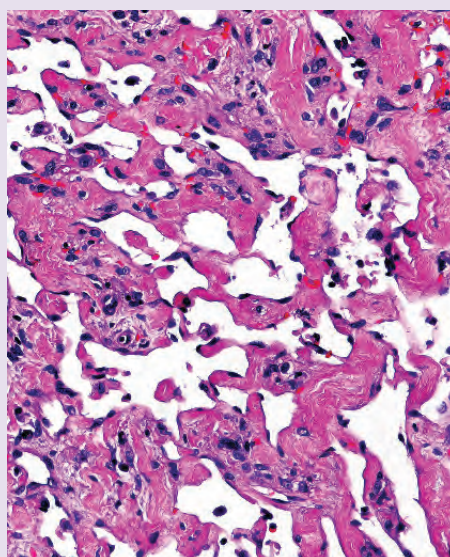
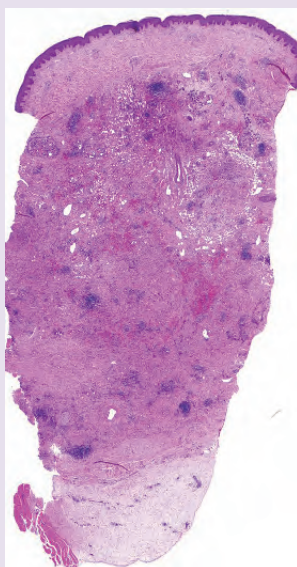
DD: Kaposi's sarcoma.

References

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Lymphangiomatosis

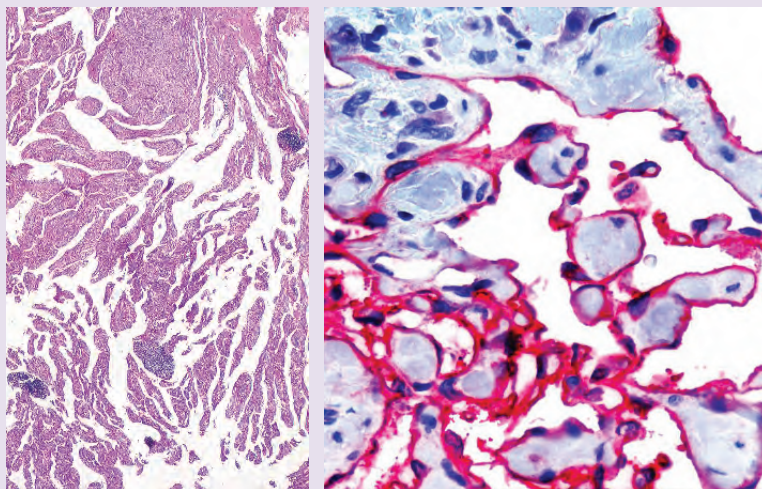
Dermal lesion, showing anastomosing lymphatic slits (right)



Lymphangiomatosis

Hair blower
pattern (left)

Podoplanin
positive
lymphatic
vessels (right)



CI: Swelling mostly of lower limbs since birth or starting early in life, produced by benign proliferation and dilation of lymph vessels. Apart from cutaneous manifestation, involvement of deep structures, bone, and viscera is possible.

Hi: Sponge-like features by anastomosing bizarre and jagged lymphatic slits and cavernous spaces in superficial and deep tissue layers without cellular anomalies. Stunning morphological similarities with tumor pattern of diffusely invasive angiosarcoma, albeit with marked lack of endothelial atypia. Importantly, endothelia of lymphangiomatosis are negative for MYC (DD: angiosarcoma) and HHV8 (DD: Kaposi's sarcoma).

DD: Angiosarcoma, Kaposi's sarcoma.

References

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Angiokeratomas

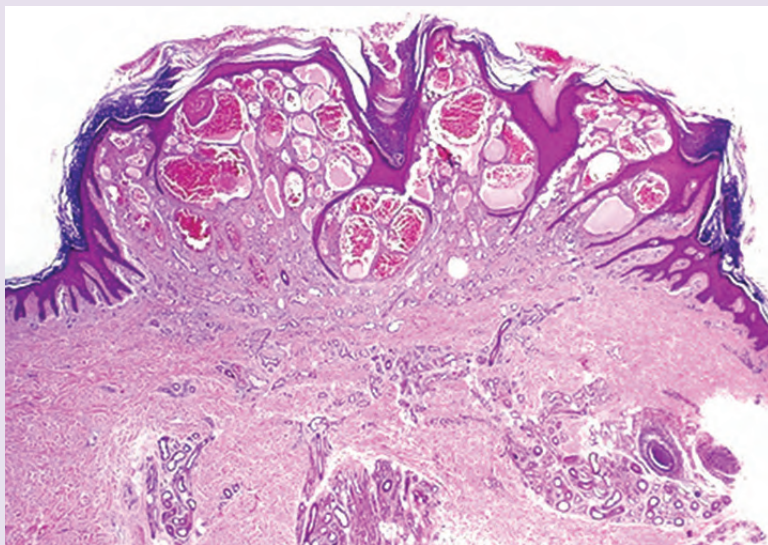
Angiokeratomas are red-blue or red-black malformations of small vessels in conjunction with massive acanthosis and hyperkeratosis at later stages of evolution. There are several variants, which differ in their clinical presentation and histomorphological correlation. Angiokeratoma is the smaller variant with exclusively subepidermally and upper dermal layer-localized thin-walled vessels, while verrucous hemangioma, as the deeper variant, shows involvement also of the deep dermis and subcutis. Remarkably, angiokeratomas of all types are vascular malformations, and as such do not regress.

Verrucous Hemangioma (Venous Malformation)

Hyperkeratotic
angiomatous
plaques with
satellite lesions
(right)



Compact
hyperkeratosis,
acanthosis,
papillomatosis
and convolutes
of capillary
and cavernous
structures in the
upper dermis



CI: Vascular malformation involving capillary and cavernous (venous) elements in superficial and deep layers of the dermis and subcutis. Hemorrhagic red plaques or papules, occasionally in linear formation, developing in early life without alterations of the epidermis. Later, during

proportionate enlargement resulting in tumorous lesions with satellites, reactive epidermal hyperplasia and verrucous hyperkeratosis occur. The legs are the preferential localisation. No tendency for spontaneous regression, in contrast to cherry angiomas.

Hi:

- Acanthosis and verrucous hyperkeratosis
- Malformative thin-walled venular vessels at all levels of the dermis, and of the subcutis
- Mid dermis may be spared: “mid-dermal grenz zone”
- Convolution of dilated venules and venous cavernous spaces
- No endothelial atypia
- Endothelia negative for WT1

DD: Angiokeratoma; capillary hemangioma; cherry angioma; verrucous melanoma.

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Clinical Variants of Angiokeratoma



Solitary angiokeratoma



Angiokeratoma
circumscriptum naeviforme



Segmental angiokeratoma
circumscriptum naeviforme



Fordyce angiokeratoma of
the scrotum



Angiokeratoma acroasphycticum
digitorum (Mibelli)

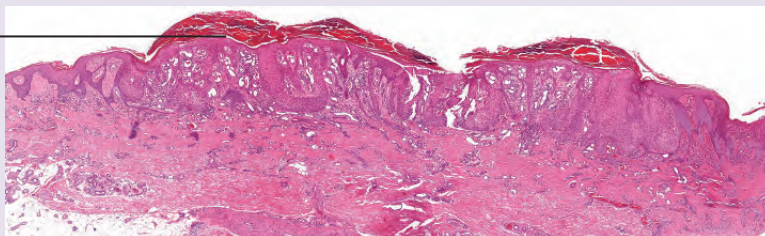


Angiokeratoma corporis
diffusum Fabry

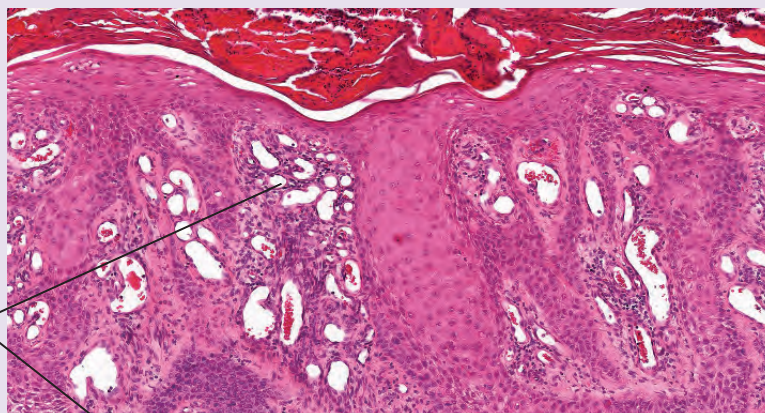
VARIANTS

Variant: Solitary Angiokeratoma

Acanthosis and papillomatosis with hyperkeratosis



Thin-walled vascular spaces in the papillary dermis



Intracytoplasmatic PAS-positive granules in endothelial cells of Fabry's disease (inset)



Cl: Solitary red-brown plaque with hyperkeratosis, preferentially on the lower extremities. There may be a history of trauma.

Hi: Epidermal hyperplasia with hyperkeratosis and dilated thin-walled vascular lacunae in the papillary dermis.

VARIANTS

Variant: Angiokeratoma Circumscriptum Naeviformis

Cl: Blue-red hyperkeratotic plaque since birth, occasionally covering a larger segmental area of the body, or following Blaschko lines.

Hi: Comparable with solitary angiokeratoma. When deeper parts of the dermis are involved, differentiation from verrucous hemangioma may be impossible.

Variant: Fordyce Angiokeratoma

Cl: Multiple small red papules on the scrotum, penis or labia major of the vulva, simulating cherry angiomas.

Hi: Comparable with solitary angiokeratoma.

Variant: Angiokeratoma Acroasphycticum Digitorum (Mibelli)

Cl: Tiny red-black hyperkeratotic spots on toes or fingers.

Hi: Comparable with solitary angiokeratoma.

Variant: Multiple "Pinpoint" Angiokeratomas (Angiokeratoma Corporis Diffusum; Fabry's Disease)

Cl: Multiple tiny red papules distributed widely over the trunk. In this particular context, angiokeratoma is a misnomer: these lesions are exclusively composed of dilated subepidermal venules in association with underlying metabolic disorders (deficiencies of galactosidase, fucosidase, and others).

Hi: Dilated subepidermal venules without acanthosis. Immunohistochemical positivity for GB3 (intracytoplasmic ceramid deposits in endothelia, nerves, smooth muscles); PAS-stained formalin-fixed – but not paraffin-embedded – cryo-sections show intracytoplasmic granules.

Variant: Acral Pseudolymphomatous Angiokeratoma of Children (APACHE)

This rare entity belongs to pseudolymphomatous reactions.

Cl: Solitary or multiple slightly hyperkeratotic red papules on the hands of children.

Hi: In the upper dermis there are nodular lymphocytic infiltrates in association with dilated small vessels.

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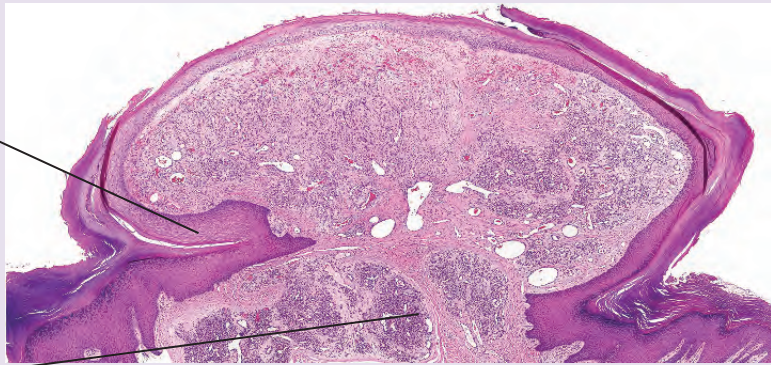
Hyperplasias

Granuloma Pyogenicum (Lobular Capillary Hemangioma; Botryomykoma)

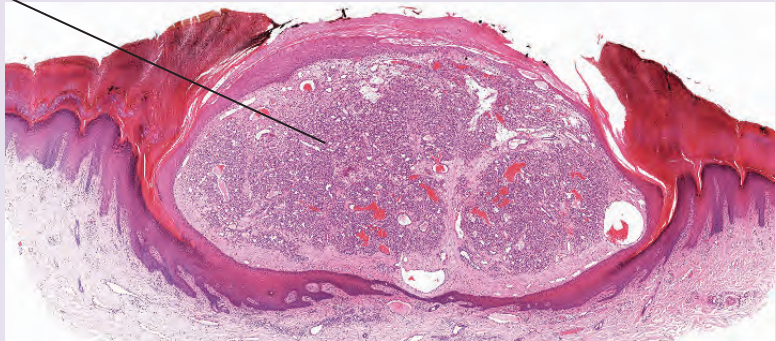
Exophytic
vascular partially
eroded lesion



Nodular lesion
with collarette of
acanthotic and
hyperkeratotic
epidermis

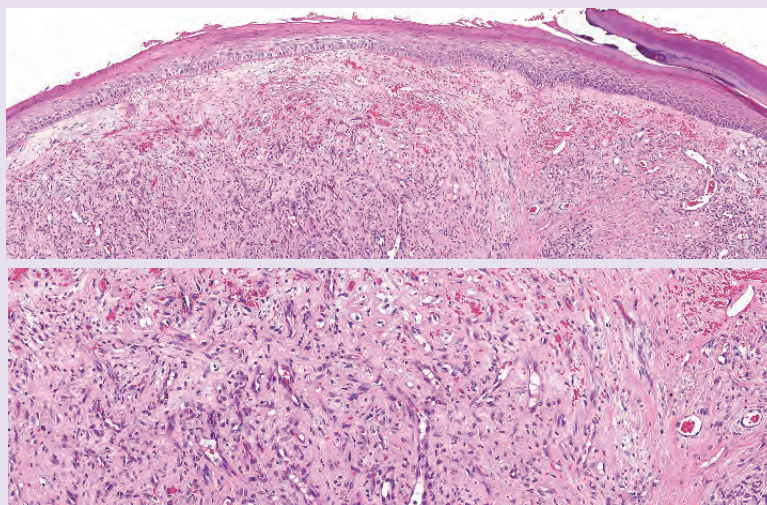


Lobular
arrangement
of capillary tufts-
separated
by broad
fibrous septa



Granuloma Pyogenicum (Lobular Capillary Hemangioma; Botryomykoma)

Mature pyogenic granuloma with marked edema and broad fibrous septa



Benign vascular tumor histologically showing a lobular structure accompanied by variable inflammatory infiltrate, without granulomatous features (the term refers to granulomatous tissue). These lesions are not neoplastic but rather reactive, following superficial injury.

Cl: Soft, friable, easily vulnerable and bleeding, peduncular exophytic nodular lesion. The small basis is surrounded by a collarette of normal surrounding skin. Fingers, palms, face, and scalp are preferential sites but it can develop on any other part of the body, including oral mucosa, possibly as a consequence of superficial trauma. The growth of the lesion can be boosted by hormonal (pregnancy) or other factors (tretinoin).

Hi:

- Dome-shaped lesion
- Epithelial collarette and epidermal lip formation on the borders
- Flat epidermis; superficial ulceration and crust formation possible
- Multilobular architecture with fibrous septae between vascular lobules
- Proliferation of capillaries (CD31, CD34): central feeding vessel
- Mitoses of endothelial cells without cellular atypia
- Variable inflammatory neutrophil-rich infiltrate and edema; fibrosis in elderly lesion

- Subcutaneous forms and extramedullary hematopoiesis in a pyogenic granuloma have been reported

DD: Granulation tissue; amelanotic malignant melanoma; capillary hemangioma; nodular Kaposi's sarcoma; angiosarcoma; acquired tufted angioma; epithelioid angiomatous nodule.

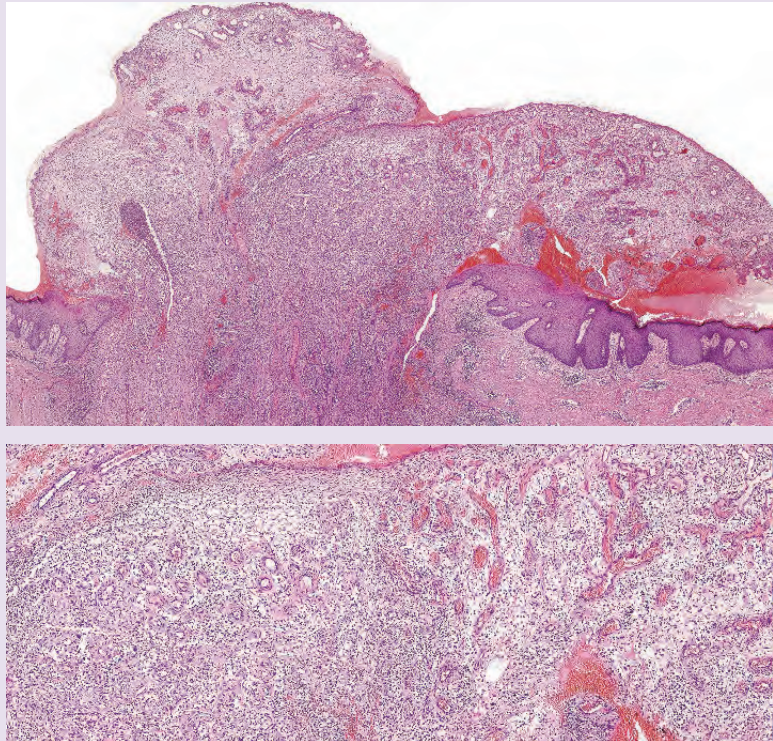
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Differential Diagnosis: Pyogenic Granuloma-Like Granulation Tissue

Protruding granulation tissue lacking the characteristic septa and capillary tufts of pyogenic granuloma



CI: Excessive, oozing proliferation of granulation tissue, occurring in wound healing and chronic ulcerations. Spontaneous regression.

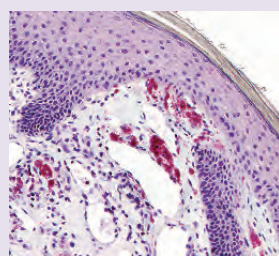
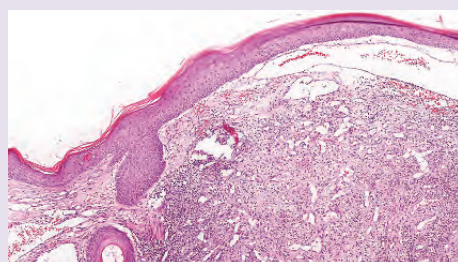
Hi: Loose suppurative granulation tissue, many capillaries, mixed inflammatory infiltrate with variable number of neutrophils.

Bacillary Angiomatosis

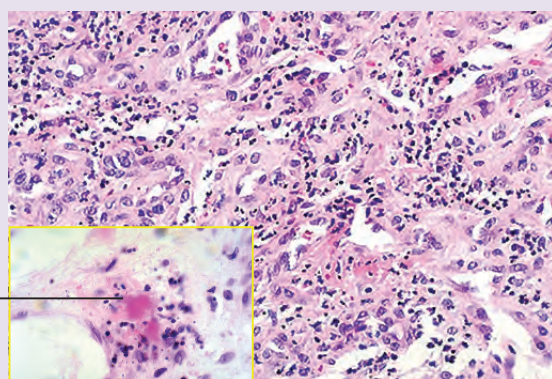
Plaques and nodules in a patient with AIDS



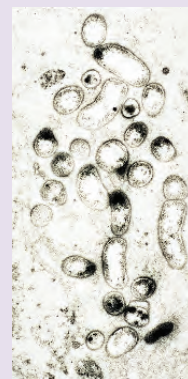
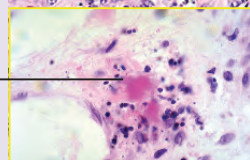
Anti-*Bartonella henselae* staining (right)



Vascular proliferation with fibrosis, neutrophilic infiltrate (mid left) and karyorrhexis (bottom)



Bacterial rods



Electron microscopy of *Bartonella henselae*

Gram negative bacteria (*Bartonella henselae* or *Bartonella quintana*; formerly *Rochalimaea*) are the causative agents in immunodeficient individuals (AIDS).

Cl: Pyogenic granuloma-like, mostly multiple red hemorrhagic nodules or plaques.

Hi:

- Vascular proliferation resembling pyogenic granuloma or granulation tissue
- Blood vessels with large, activated epithelioid endothelia, high mitotic activity

- Conspicuous lack of fibrous septa between capillary lobules
- Edematous stroma
- Neutrophil-rich inflammatory infiltrate with karyorrhexis
- Causative bacteria can be demonstrated by Warthin–Starry stain or immunostains

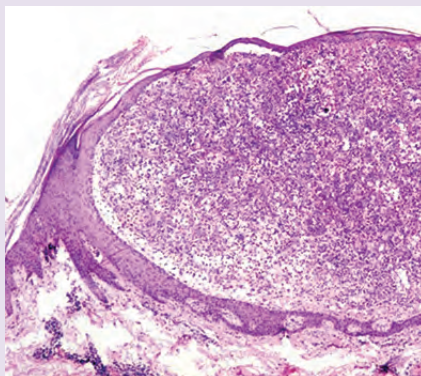
DD: Pyogenic granuloma (lobular capillary hemangioma); epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia); Kaposi's sarcoma; verruga Peruana.

References

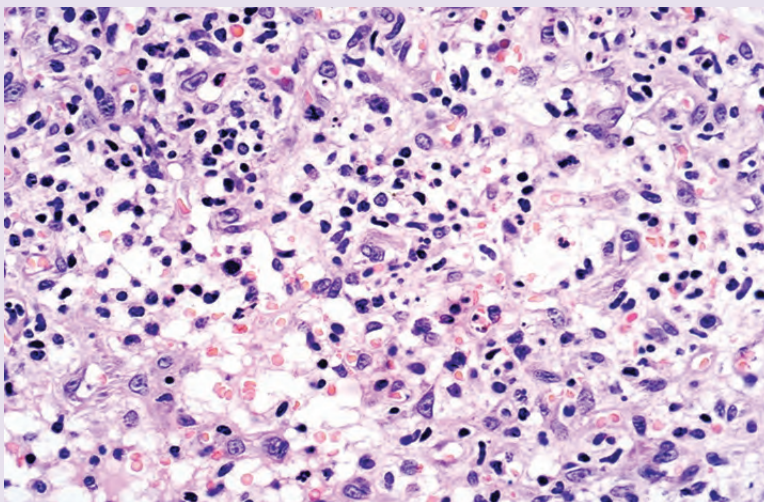
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Verruga Peruana

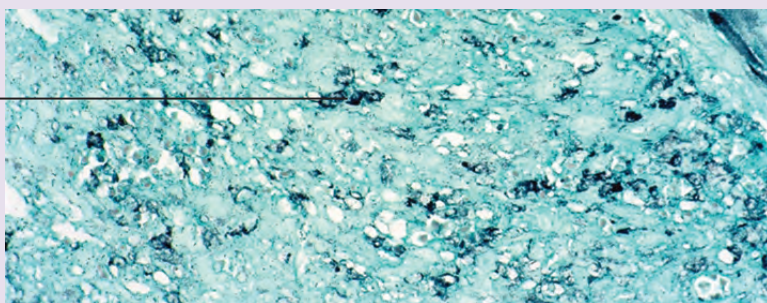
Multiple nodules on the legs



Vascular proliferation and inflammatory infiltrate in an edematous, inflammatory stroma (upper right and mid)



Bartonella bacilliformis. Grocott stain



CI: Dermal papules and nodules, pedunculated, eroded or verrucous, resembling bacillary angiomatosis; due to infection by *Bartonella bacilliformis* in the Andes Mountains of South America, transmitted by sandflies.

Hi: Corresponds to bacillary angiomatosis, albeit with exclusively intracytoplasmic bacteria (Rocha-Lima bodies).

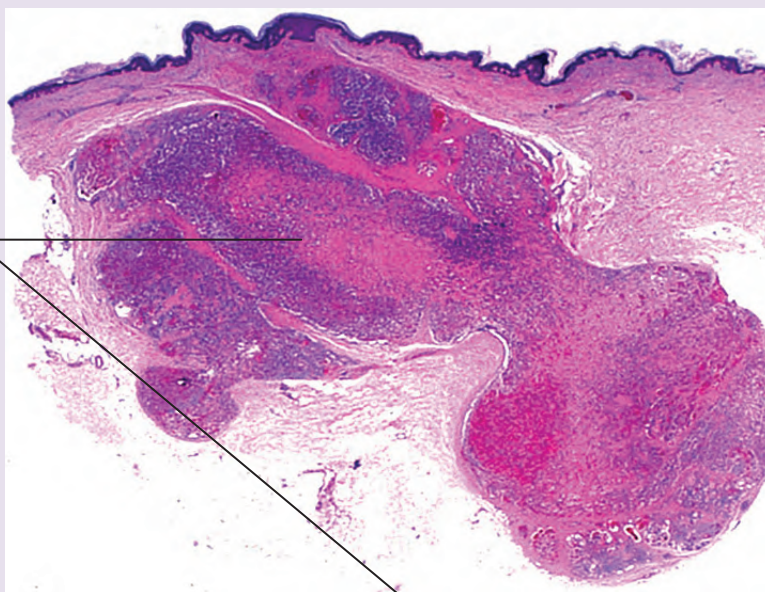
DD: See bacillary angiomatosis.

Reference

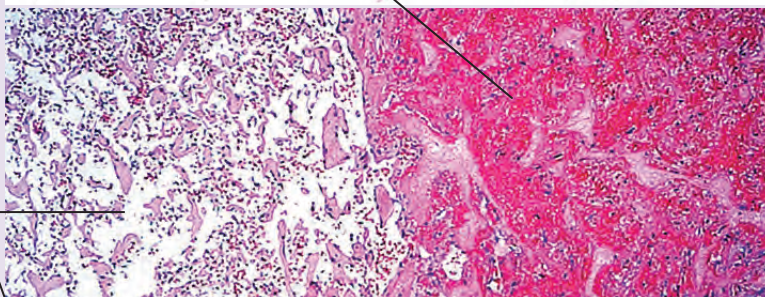
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Intravascular Papillary Endothelial Hyperplasia (Masson)

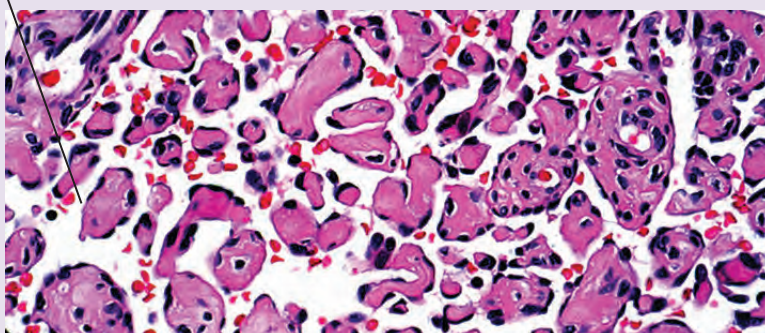
Intravascular
organized
thrombus



Anastomizing
capillary
spaces with
endothelial
folds and
septa



Regular
endothelia
without atypia



CI: This distinct reaction pattern was described by Masson 1923 as a vegetant intravascular angiosarcoma-like proliferation in thrombi of hemorhoidal veins. It appears as subcutaneous violaceous nodular swelling preferentially on head, neck, and extremities but also in other localisations. Not necessarily associated with a pre-existing vascular lesion but can occur in a thrombosed blood vessel or within a vascular tumor or malformation.

Hi:

- Intravascular papillary endothelial proliferations in a thrombus undergoing organization and hyalinization
- Always within a pre-existing vessel (mostly veins); in exceptional cases “spilling over” into the adjacent dermis
- Anastomosing and labyrinthian vascular spaces, lined with flattened endothelial cells (endothelial septa and folds)
- Hyalinized papillary blebs and fibrous cores coated by endothelial cells
- Advanced stages with accompanying alpha smooth muscle actin-positive outer pericytic layers
- Myofibroblasts in the stroma
- Lack of cellular atypia

DD: Angiosarcoma; glomeruloid hemangioma; endovascular papillary angioendothelioma (Dabska tumor).

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Acroangiokeratosis Mali (Pseudo-Kaposi’s Sarcoma)

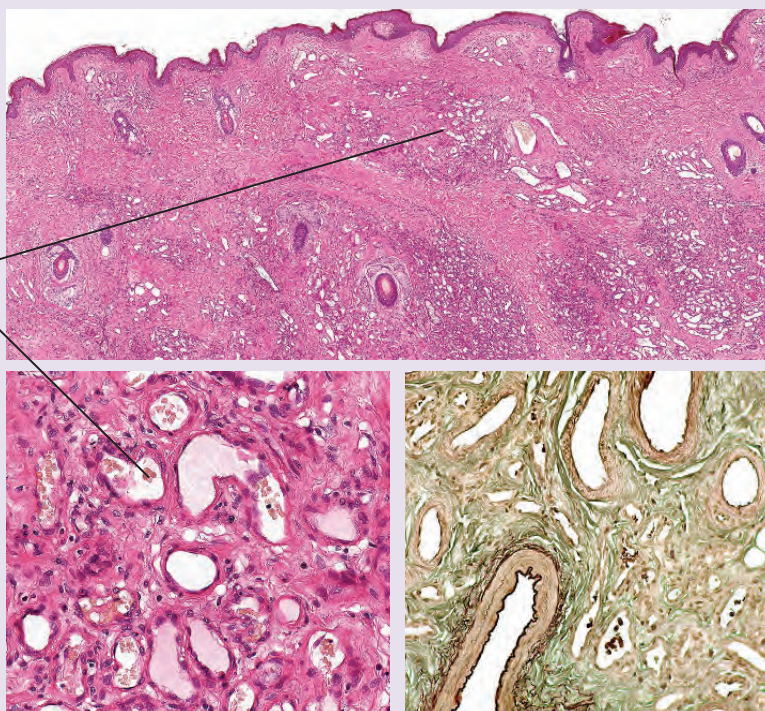
Red-violaceous plaques



Acroangiodermatitis Mali (Pseudo-Kaposi's Sarcoma)

Convolutes of
dilated
capillaries with
characteristic
lobular
arrangement

Van Gieson stain
showing venous
feeder vessels
(right)



Cl: Blue-red or violaceous lichenoid macules and plaques in chronic venous insufficiency and venous stasis of the lower extremities, ankles, and toes. Similar lesions are seen in arteriovenous malformation or hemodialysis shunt.

Hi:

- Epidermal hyperplasia, occasionally verrucous hyperkeratosis
- Edema and subsequent fibrosis in the upper and mid dermis
- Proliferating capillaries convoluted and dilated in a markedly lobular arrangement
- Plump endothelial cells
- No cellular atypia; no mitoses
- Extravasation of erythrocytes
- Deposits of hemosiderin in siderophages
- Chronic inflammation

DD: Kaposi's sarcoma; pyogenic granuloma.

References

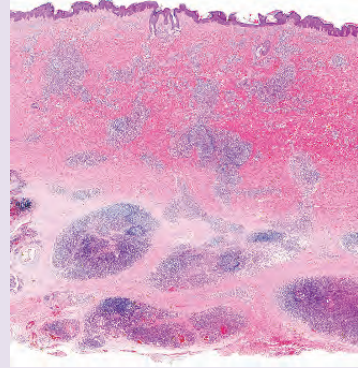
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Benign Vascular Neoplasms

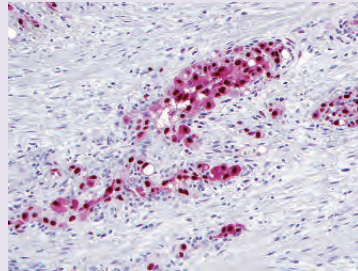
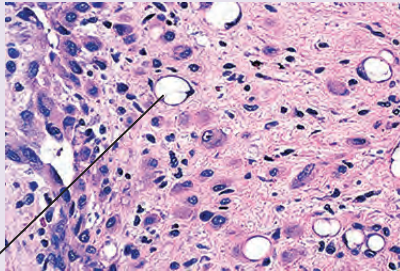
Epithelioid Hemangioma (Angiolymphoid Hyperplasia with Eosinophilia, ALHE)

Multiple nodules on the earlobe (left)

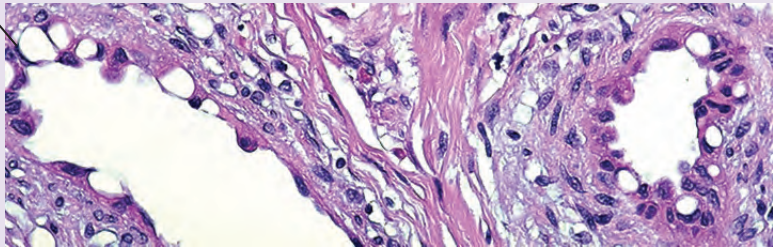
Reactive lymphoid follicles surrounding vascular proliferations (right)



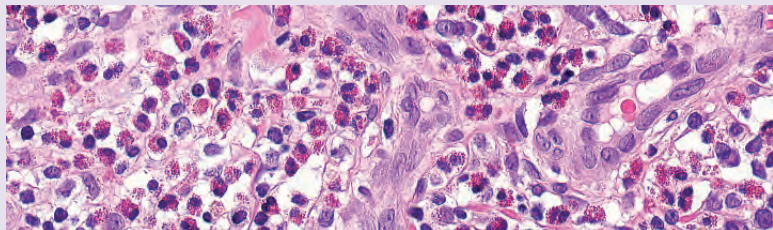
FOS-B positive epithelioid cells (right)



Plump epithelioid endothelial cells with vacuoles



Accompanying eosinophilic infiltrate



Various forms of epithelioid vascular tumors have to be differentiated: (1) epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia), which is benign and is not related to HHV-8 infection; (2) epithelioid hemangioendothelioma, which is low grade malignant; and (3) epithelioid

angiosarcoma, which represents high-grade malignancy.

It is still a matter of debate whether ALHE is a reactive vascular proliferation or a primary benign vascular tumor. Recently, ALHE has been subsumed under the umbrella term *epithelioid*

hemangioma that includes various morphological variants of benign hemangioma with epithelioid endothelial cells. Erroneously, the term *Kimura's disease* is sometimes used synonymously with angiolymphoid hyperplasia with eosinophilia. However, these diseases are nosologically and histologically totally unrelated.

Cl: Multiple grouped asymptomatic red nodules with a smooth surface, typically on the head and on the external earlobe.

Hi: Benign epithelioid hemangioma comprises superficial and deep variants of ALHE and classic solitary or multicentric solid epithelioid hemangioma. The common denominator is an epithelioid endothelial cell, sometimes with intracytoplasmic vacuoles ("blister cell") and immunohistochemical positivity for FOS-B.

- *Deep type of ALHE:* thick-walled venular vessels with prominent epithelioid endothelia. At the outer margin, there are eosinophil-rich lymphoid follicles
- *Superficial type of ALHE:* small protuberant papules with venular vessels in the upper and mid dermis. Epithelioid endothelia. Eosinophil-rich inflammatory infiltrate
- *Solid type of ALHE:* aggregated vessels with collapsed lumina. Predominance of epithelioid endothelia, sometimes in long rows or strands, simulating epithelioid hemangioendothelioma
- Large epithelioid endothelial cells without pleomorphism
- "Blister cells": endothelial cells with intracytoplasmic vacuoles
- Immunophenotype: FOS-B positive endothelia, rarely co-expressing cytokeratins

DD: Pyogenic granuloma; Kimura's disease; epithelioid hemangioendothelioma; epithelioid angiosarcoma; cutaneous epithelioid angiomatous nodule.

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ENDOTHELIAL DIFFERENTIATION

Endothelial Differentiation

Infantile Capillary and Congenital Hemangioma

Superficial (left)
and deep (right)
hemangiomas

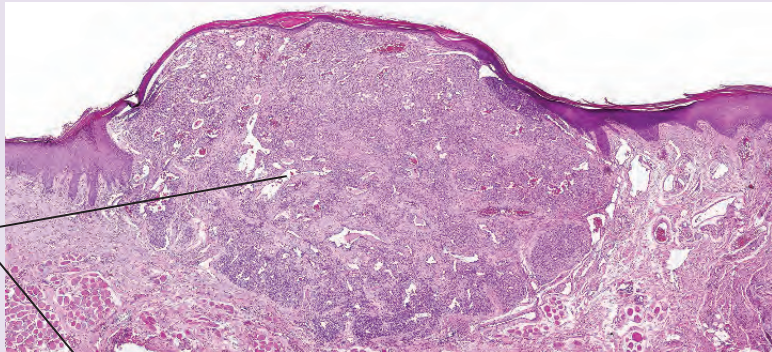


Cl: Common benign vascular tumor present at birth or acquired within the first weeks of life in 1% of newborns. Infantile and congenital hemangioma present as red or bluish erythemas, patches, and nodules of variable size, with marked predominance of the small-nodular type. Rapid enlargement before

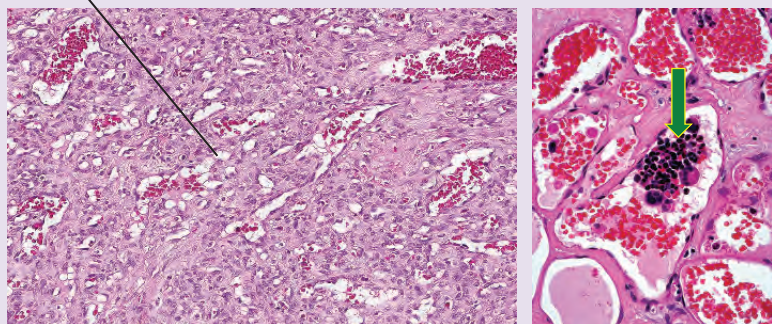
spontaneous regression within 4–8 years. Regression is indicated by replacement of the red color (blood vessels) by whitish fibrosis. Capillary hemangiomas are red and more superficial. Cavernous hemangiomas tend to be more bluish due to the deeper localization of wider vascular spaces.

Infantile Capillary and Congenital Hemangioma

Lobules of
capillaries
and venules



Extramedullary
hematopoiesis
in a regressing
lesion (arrow
right)



ENDOTHELIAL DIFFERENTIATION

Hi: Lobular lesion with circumscribed borders, albeit with frequent multicentricity. While early lesions may be very cellular with densely packed capillary vessels and few patent lumina, late lesions may be hypocellular with isolated capillary lobules and massive fibrosis (signs of regression). No cellular atypia, regular capillary vessel walls. Differentiation between infantile hemangioma (GLUT1-positive endothelia) and congenital hemangioma (GLUT1-negative endothelia) is paramount, mostly for clinical reasons. Congenital hemangioma is further subdivided into NICH (non-involuting) and RICH (rapidly involuting) variants.

DD: Angiosarcoma; kaposiform hemangioendothelioma; tufted hemangioma.

References

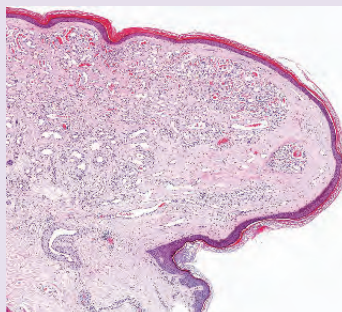
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Cherry Angioma (Senile Hemangioma)

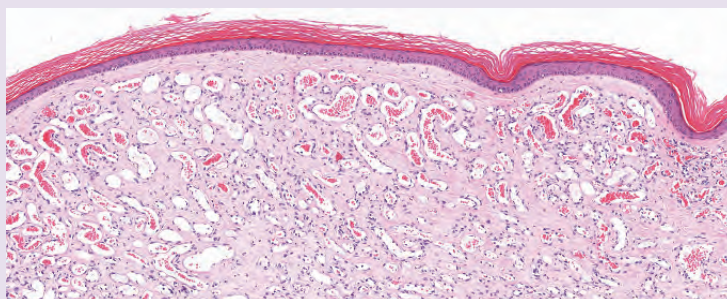
Multiple cherry ("senile") angiomas on the trunk (left)



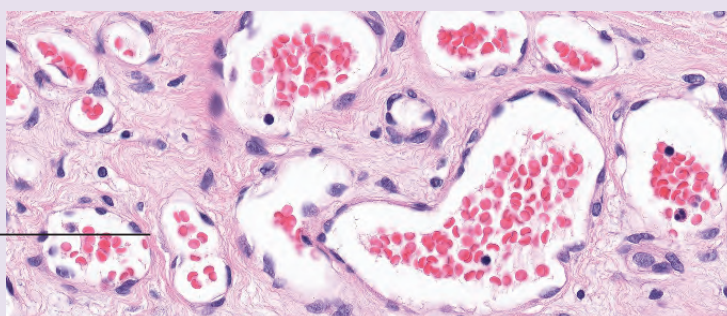
Lobules of dilated venules in an exophytic lesion (right)



Ectatic capillaries in the upper and mid dermis



Fibrous septa between ectatic vessels



ENDOTHELIAL DIFFERENTIATION

Cl: Common finding appearing in midlife and increasing in number with age, often multiple. Trunk but also any other localisation. Tiny, multiple disseminated deep-red skin papules or macules.

Hi: Exophytic lesions consisting of small lobules of thin-walled endothelial vessels and vascular channels, separated by fibrous septa. Overlying epidermis may be flattened.

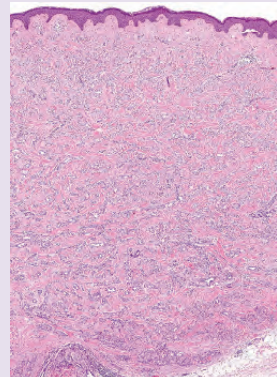
DD: Angioma serpiginosum; pyogenic granuloma.

References

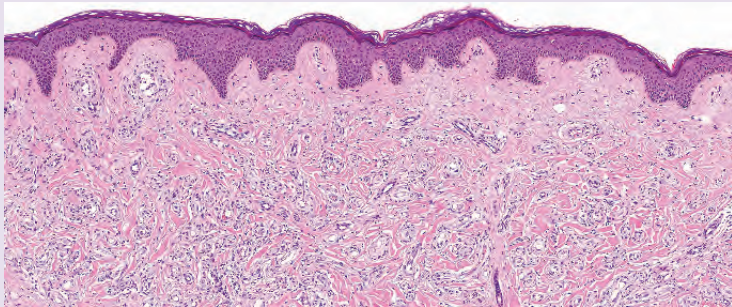
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Microvenular (Microcapillary) Hemangioma

Plaque on the trunk



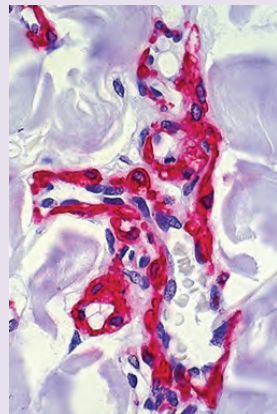
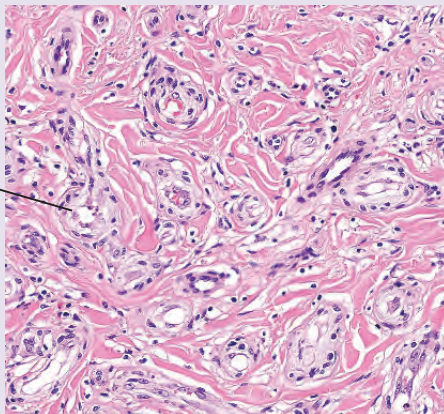
Small venules in a markedly diffuse arrangement (top right and mid)



Small venules with thick cuffs of surrounding pericytes

Cuffs of ASMA positive pericytes (right)

Background of densely packed fibrous stroma



ENDOTHELIAL DIFFERENTIATION

Cl: Mostly solitary, small, slowly enlarging purple or red-brown nodule or plaque lesion in young to middle-aged adults.

Hi:

- Diffuse, non-lobulated proliferation of multiple small blood vessels with thickened outer vessel walls
- Moderately fibrotic stroma
- Inconspicuous layer of alpha smooth muscle actin-positive pericytes (hallmark of venular differentiation) around these vessels (differentiation from angiosarcoma and Kaposi's sarcoma)
- No pleomorphism or mitoses
- Endothelia are negative for HHV8 and MYC

DD: Capillary hemangioma; tufted hemangioma; Kaposi's sarcoma; sclerosing hemangioma (dermatofibroma).

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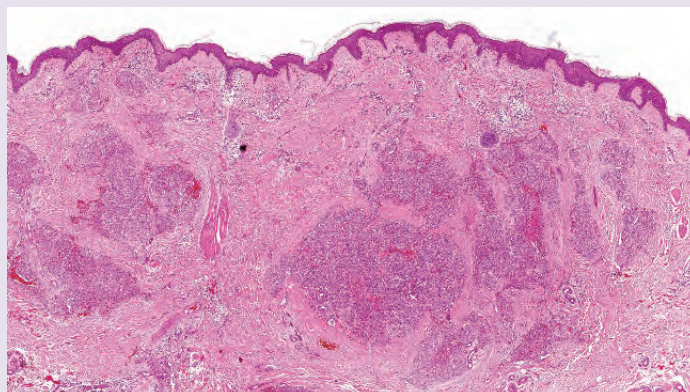
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Tufted Angioma

Erythema with “tufts” of protruding vascular proliferations



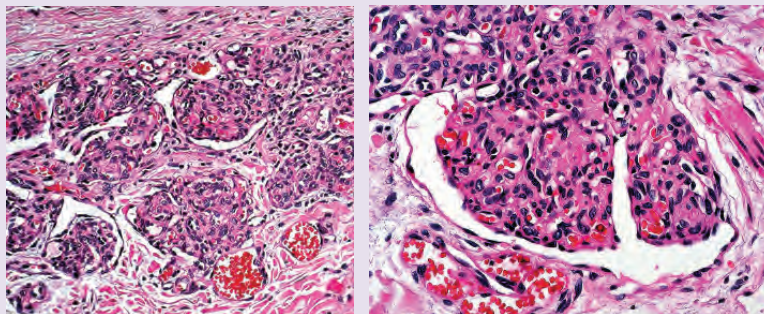
Typical “cannon-ball” pattern composed of capillary and microvenular vascular lobules throughout the dermis



ENDOTHELIAL DIFFERENTIATION

Tufted Angioma

Venular half-moon-like spaces at the periphery of capillary lobules (left and right)



Tufted hemangioma (TH) and kaposiform hemangioendothelioma (KH) are closely related vascular tumors; kaposiform hemangioendothelioma is considered to be the deep variant of tufted hemangioma. Both tumors may be associated with Kasabach–Merritt syndrome.

Cl: Rare tumor present at birth or developing in the first years of life, presenting as flat red-brown bruise-like slowly growing macules, patches or papular lesions of variable size, preferentially in the head, neck or upper trunk areas. Spontaneous regression may occur.

Hi:

- Multicentric roundish sharply circumscribed nodules of capillaries
- Dissemination of small capillary lobules throughout the dermis (“cannonball pattern”)
- All levels of the dermis involved, extending into the subcutis
- Slit-like dilated blood vessels in half-moon arrangement at outer periphery of capillary lobules
- Regular capillary vessels
- No inflammatory infiltrate
- No cellular atypia
- Focal thromboses may occur (hallmark of Kasabach–Merritt syndrome)
- No deposits of hemosiderin

Immunohistochemistry: CD31-positive endothelia and alpha smooth muscle actin-positive pericytes. Importantly, both TH and KH express foci of strong positivity for podoplanin

(marker of endothelia with lymphatic differentiation).

DD: Granuloma pyogenicum; infantile capillary hemangioma; glomeruloid hemangioma.

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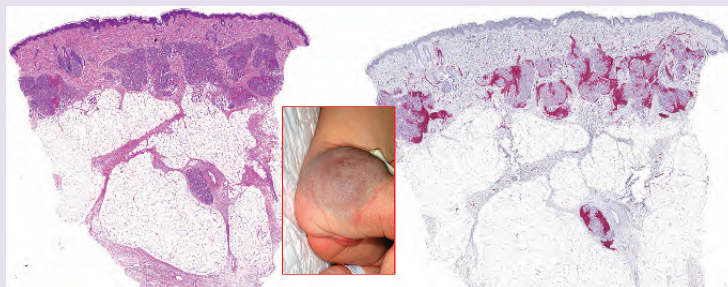
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ENDOTHELIAL DIFFERENTIATION

Kaposiform Hemangioendothelioma

Nodular infiltrate in the dermis and the subcutis (left); podoplanin positive (right)

Inset: large hemangioma on the hip of a child



Lethal outcome has been reported in 50% of patients due to the aggressive and invasive growth, and massive thrombocytopenia and consumption coagulopathy in the context of Kasabach–Merritt syndrome.

CI: Rare vascular neoplasm in children and occasionally in adults. Considered to be the deep variant of tufted hemangioma. The deep

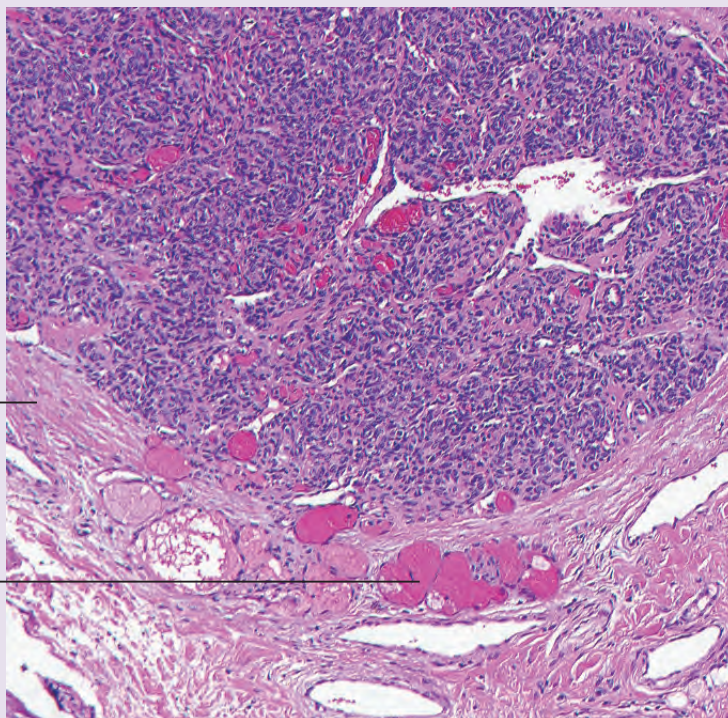
soft tissue, especially the retroperitoneum, is involved and particularly the skin in 75% of patients. In the skin, ill-defined violaceous masses, reaching into the deep tissue levels, and purpuric lesions are found. Frequent association with Kasabach–Merritt syndrome. The tumor may be multifocal but does not metastasize.

Kaposiform Hemangioendothelioma

Nodular proliferation of endothelial cells

Septa of fibrous tissue

Vascular slits, channels and lacunae with fibrin thrombi



ENDOTHELIAL DIFFERENTIATION**Hi:**

- Involvement of the dermis and subcutis
- Capillary lobules and sheets with peripheral half moon-shaped spaces
- Vascular cannonball pattern and sheets of densely aggregated capillaries and spindled myofibroblasts

- No cytological atypia
- Multifocal fibrin thrombi within vascular lumina, as indicators of Kasabach–Merritt syndrome

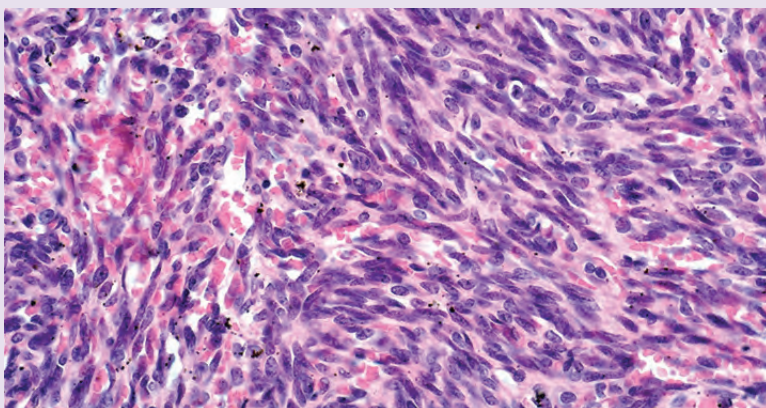
Immunohistochemistry: Multifocal positivity for podoplanin, similar to tufted hemangioma.

Kaposiform Hemangioendothelioma (with Kasabach-Merritt Syndrome)

Abdominal tumor (left) and plaque-like lesions on the leg (right)



Proliferation of spindle cells. Erythrocyte extravasation

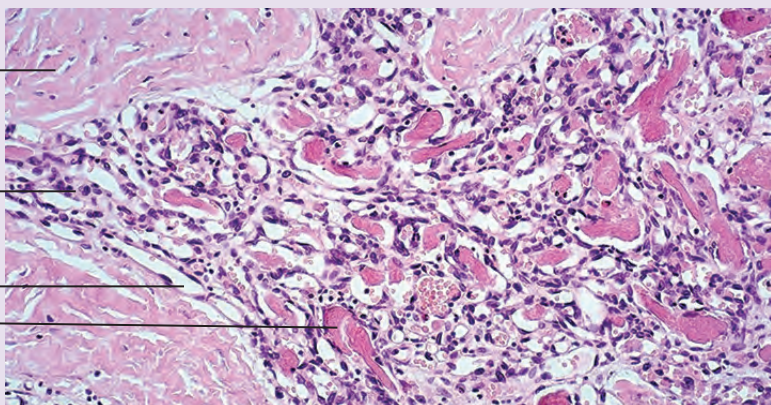


Fibrous septa

Regular endothelial cells

Elongated vascular channels.

Fibrin thrombi



ENDOTHELIAL DIFFERENTIATION

DD: Kaposi's sarcoma; capillary hemangioma; spindle cell hemangioma; tufted angioma.

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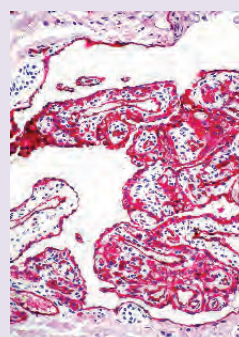
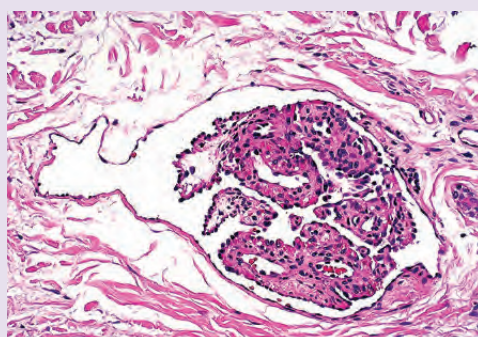
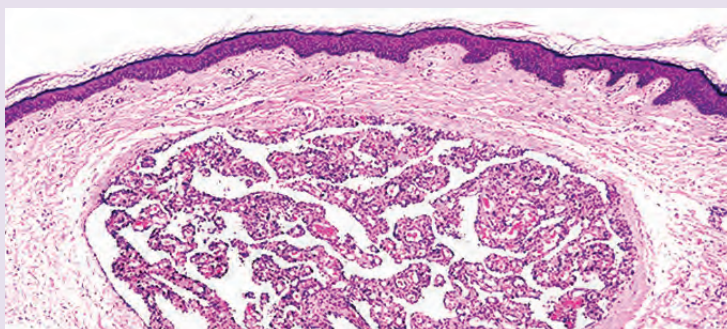
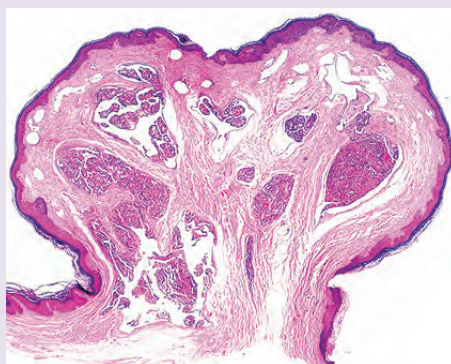
Glomeruloid Hemangioma in POEMS Syndrome

Multiple red papules on the trunk (left)

Ectatic vascular spaces, surrounding intraluminal conglomerates of capillaries, resembling renal glomeruli (right top and mid)

Intravascular “glomeruli” (mid and bottom left)

CD 31-staining (right)



ENDOTHELIAL DIFFERENTIATION

Cl: This type of angioma, which histologically simulates renal glomeruli, presents as single or multiple red papules and is associated with POEMS (polyneuropathy, organomegaly, endocrine disorders, **M** protein, and skin changes) syndrome. Prevalence in Japanese ethnics.

Hi:

- Ectatic vascular spaces, surrounding intraluminal conglomerates of “free-floating” capillaries, resembling renal glomeruli
- Mostly flat, occasionally plump endothelial cells
- Presence of eosinophilic globules in some cases
- PAS-positive inclusions in some endothelial cells (immunoglobulins)
- Sinusoidal spaces

DD: Acquired tufted angioma; intravascular pyogenic granuloma; intravascular proliferation in cryoglobulinemia; reactive angioendotheliomatosis; papillary intralymphatic angioendothelioma (Dabska tumor); nodular Kaposi’s sarcoma.

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Pericytic Differentiation

Solitary fibrous tumor is a nodular lesion with the clinical aspect of a dermatofibroma, cyst or adnexal tumor. There are multiple sites, including the mucosa. *Myopericytoma* and *infantile myofibromatosis* are plaque-like tumors, often with a hemangioma-like or dermatofibroma-like morphology. In infants, regression may occur. Poorly vascularized and myofibroblast-rich variants are called *myofibroma*.

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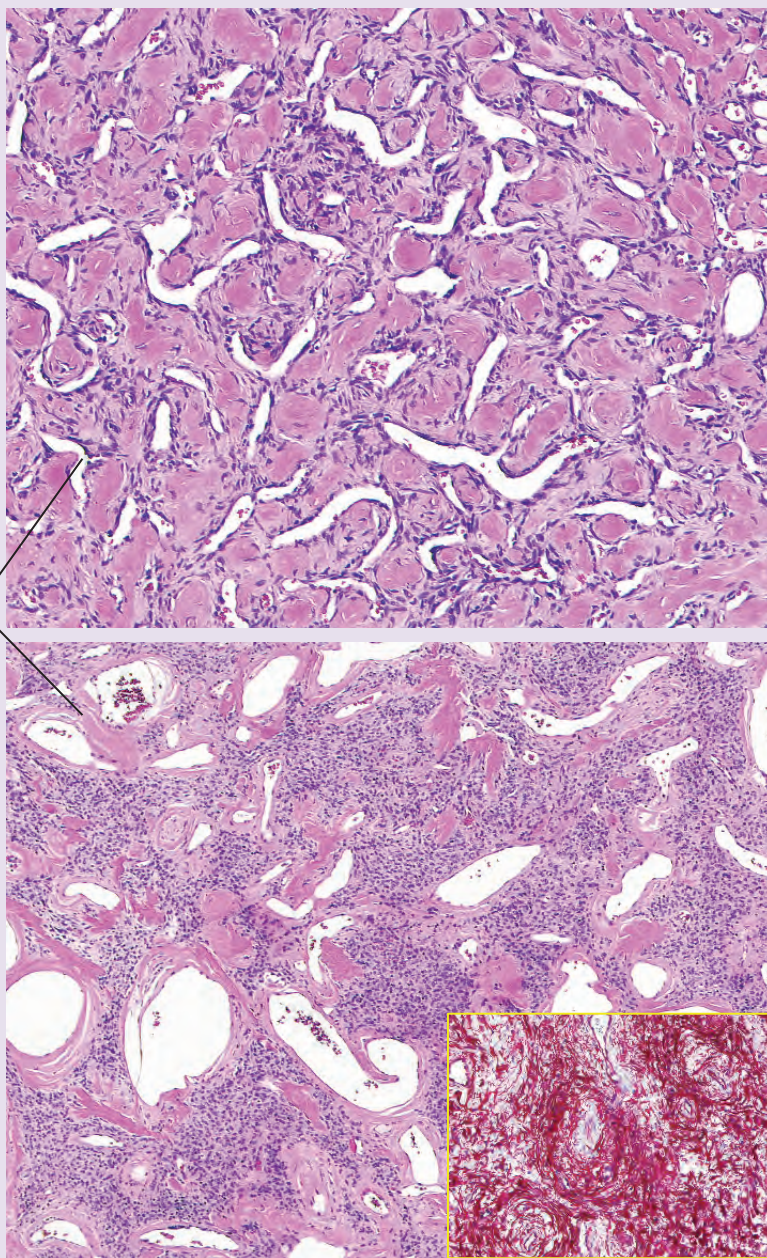
PERICYTIC DIFFERENTIATION**Imitator: Solitary Fibrous Tumor of the Skin (SFT)**

Solitary fibrous tumor is an imitator of pericytic differentiation.

Solitary Fibrous Tumor of the Skin

Staghorn-like vessels with broad sclerotic rims

Inset:
perivascular fibrosis (CD34)



PERICYTIC DIFFERENTIATION

Cl: The most common localisation is the pleura but extrapleural localisations such as the mucosa and the head and neck area of the skin have been reported. These tumors formerly were subsumed under the umbrella term *hemangiopericytoma*.

Hi:

- Broad spectrum of histo- and cytomorphological presentation (“patternless pattern”)
- Hypo- and hypercellular areas
- Prominent hemangiopericytoma-like pattern: antler-like branching of vascular spaces
- Perivascular eosinophilic sclerotic rims

Immunohistochemistry: STAT6 and CD34.

DD: Hemangiopericytoma; myopericytoma; dermatofibroma; dermatofibrosarcoma protuberans.

References

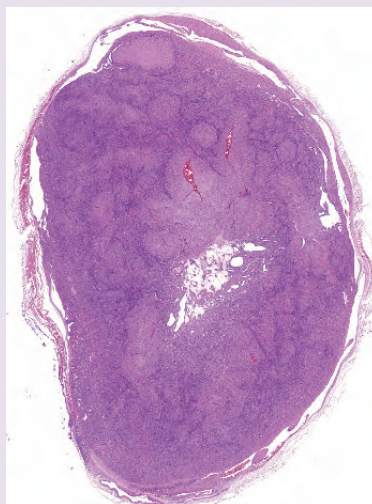
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Myopericytoma (Infantile Myofibromatosis; Perivascular Myoma (incl. Myofibroma))

Perivascular tumors, evolving from pericytes and myogenic cells of the external vessel wall. Infantile myofibroma, adult myofibroma, and infantile myofibromatosis are closely related morphological variants of the same entity.

Myopericytoma

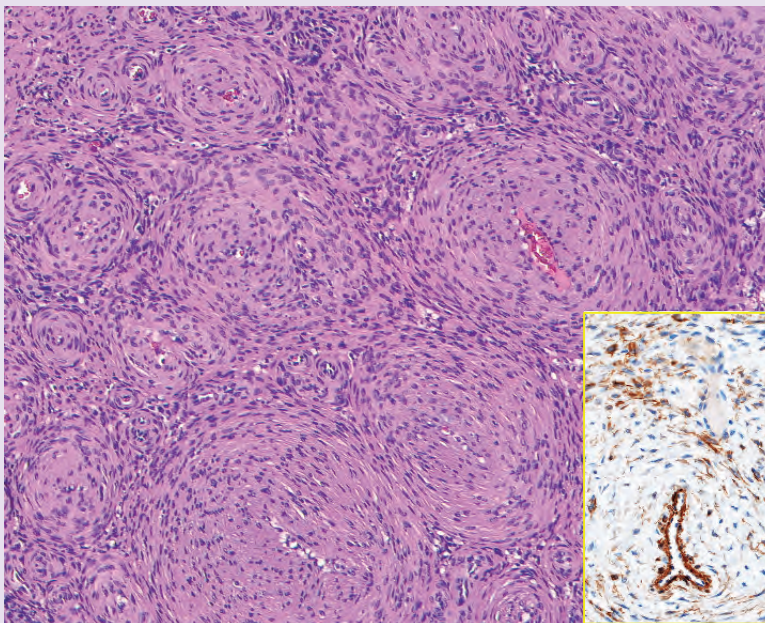
Nodular tumor on the trunk (left), sharply demarcated but not encapsulated (right)



PERICYTIC DIFFERENTIATION**Myopericytoma**

Bizarre blood vessels surrounded by plump spindled myoid tumor cells

CD34-positive endothelia and interspersed fibroblasts (inset)



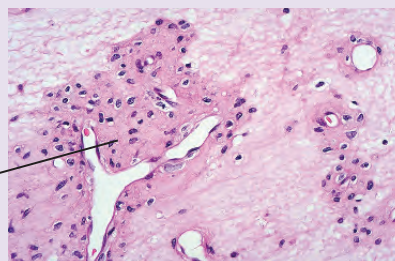
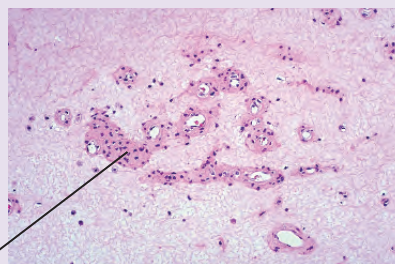
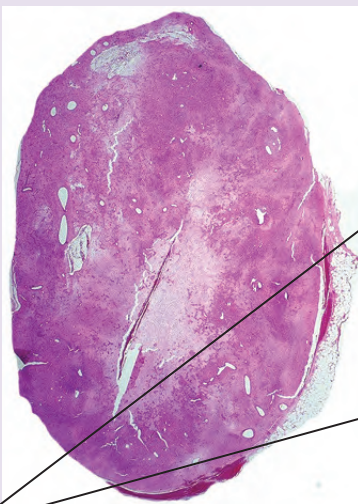
CI: Solitary or multiple firm cutaneous or subcutaneous nodules or plaques.

Myofibroma

Sharply circumscribed nodule (left)

Richly vascularized nodule with sclerotic stroma (right)

Pericytes "spinning off" the myoid wall of venular vessels



PERICYTIC DIFFERENTIATION**Hi:**

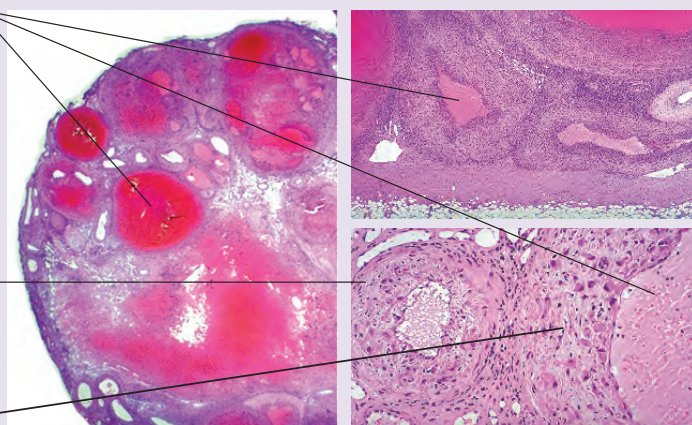
- Solitary or multicentric nodular tumors
- Richly vascularized sheets of small pericytic cells (positive for alpha smooth muscle actin)
- Intermingled deeply basophilic hypocellular nodules with pseudochondroid stroma and spindled myofibroblasts
- Adjacent staghorn-like, thin-walled vessels
- Characteristic “spinning off” of small fascicles of pericytes from the outer vessel walls
- In infantile myofibromatosis, “inversed zonation” versus adult and solitary myopericytoma, with peripheral vessels and internal basophilic nodules in the former
- In adult and solitary myofibroma, predominance of desmin-negative myofibroblasts

Variant: Atypical/Symplastic Myopericytoma with Marked Cytological Atypia

Lacunae filled with blood

Perivascular tumor cells

Atypical “symplastic” pericytes in outer vessel wall



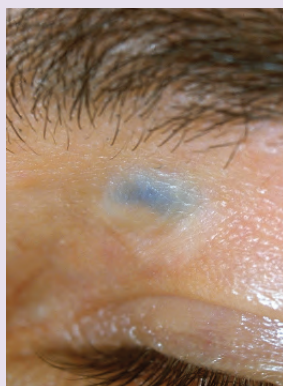
DD: Hemangiopericytoma; glomus tumor; angioleiomyoma.

Reference

Requena, L., Kutzner, H., Hugel, H., Rutten, A., and Furio, V. (1996) Cutaneous adult myofibroma: a vascular neoplasm. *J Cutan Pathol* **23**(5): 445–57.

Glomoid and Myoid Differentiation**Glomus Tumor**

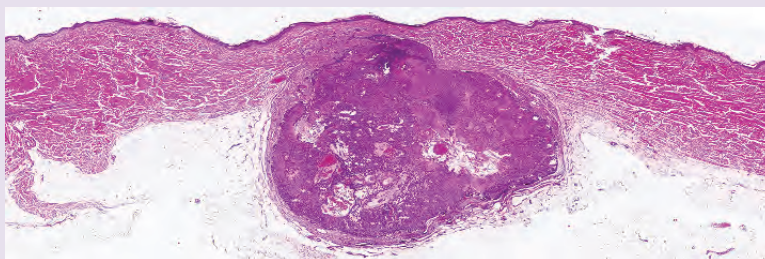
Bluish subcutaneous nodule on the forehead (left) and subungual (right)



GLOMOID AND MYOID DIFFERENTIATION

Glomus Tumor

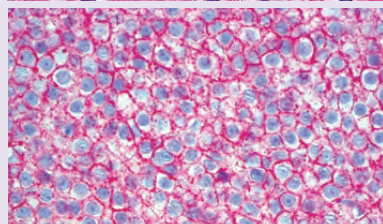
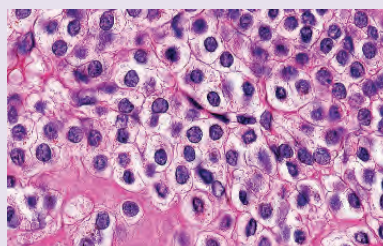
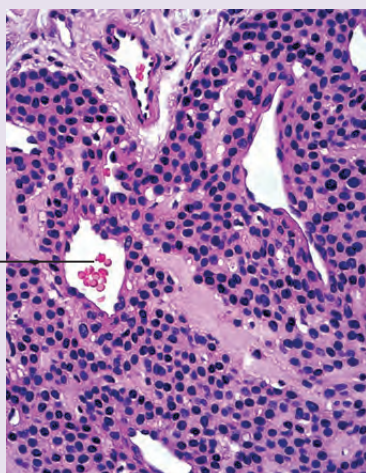
Well circumscribed encapsulated subcutaneous nodule



Solid sheets of uniform cuboidal glomus cells (left)

Small dilated venules

Sheets of glomus cells (right top), surrounded by rims of collagen IV (right bottom)



Glomus tumor is a genuine tumor composed exclusively of glomus cells, while glomuvenular malformation (obsolete term *glomangioma*) is a venous malformation with adjacent glomus cells in the outer vessel walls. The terms *glomus tumor* and *glomangioma* refer to the neuromyoarterial shunt (“glomera cutanea”), found preferentially in the reticular dermis of the nail-beds, toes, fingers, and other distinct anatomical sites. They regulate the blood flow in arteriovenous anastomoses and are composed of glomus cells, myoid spindle cells, and blood vessels. Genetic underpinnings of proliferations with glomus cells may be found in mutations of the glomulin gene.

CI: Solitary or multiple small bluish subcutaneous pressure-sensitive or spontaneously painful nodule, preferentially in a subungual localisation. Multiple lesions may present as larger congenital

plaques. Malignant variants (glomangiosarcoma or malignant glomus tumor) are rare.

Hi:

- Normal epidermis
- Monomorphous round or cuboidal glomus cells (alpha smooth muscle actin positive) surrounded by collagen IV-positive outer collagenous rims
- No pleomorphism or mitoses
- Variants:
 - Large vascular spaces, incompletely lined by glomus cells in the outer vascular layer (glomuvenular malformation)
 - Solid sheets of cuboidal glomus cells (solid glomus tumor); myxoid variants are CD34 positive
 - Predominance of spindle-shaped smooth muscle cells in conjunction with banal glomus cells (glomangiomyoma)

GLOMOID AND MYOID DIFFERENTIATION

DD: Blue rubber bleb nevus syndrome; painful vascular or soft tissue tumors; mastocytoma; adnexal tumors (eccrine acrospiroma; nodular hidradenoma); melanocytic nevus; Merkel cell carcinoma.

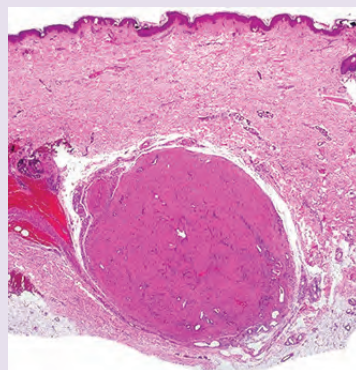
References

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Angioleiomyoma (Angiomyoma; Vascular Leiomyoma)

Solitary painful nodule on the toe (left)

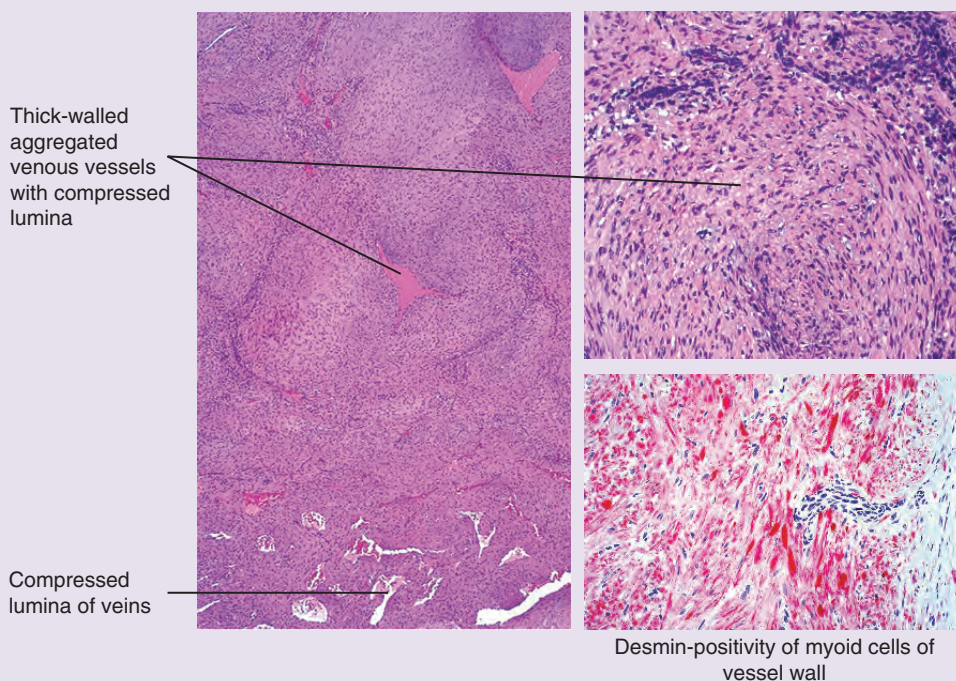
Well circumscribed solid myoid nodule extending into the subcutis (right)



CI: Benign solitary blue-red firm cutaneous nodules, preferentially located on the legs and feet of adult women. Painful, spontaneously or upon pressure. Recently, angioleiomyoma has

been subsumed under the heading of the myoid perivascular tumors, including glomus tumor, and myopericytoma/myofibroma.

Angioleiomyoma (Angiomyoma; Vascular Leiomyoma)



Hi:

- Well-circumscribed solid nodule in the cutis or subcutis
- Composed of confluent thick-walled veins with collapsed lumina
- Myoid spindle cells positive for desmin

DD: Leiomyosarcoma; pilar leiomyoma; myopericytoma; pleomorphic angioleiomyoma; hyalinized angioleiomyoma; adult myofibroma; angiolipoleiomyoma.

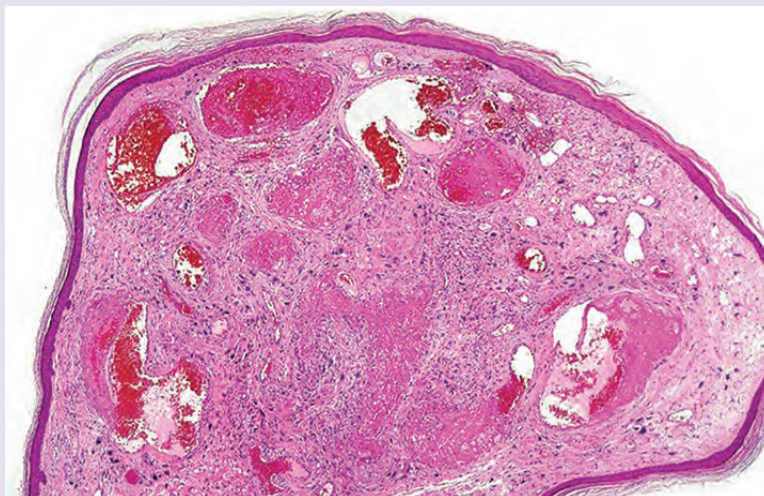
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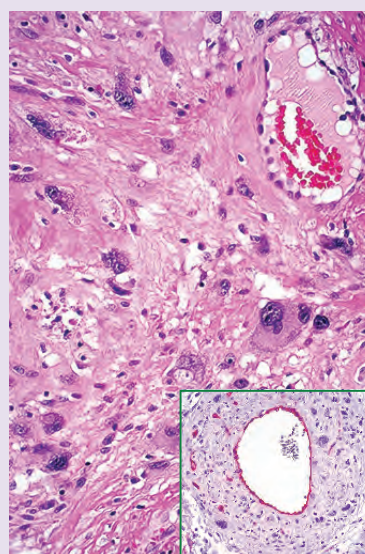
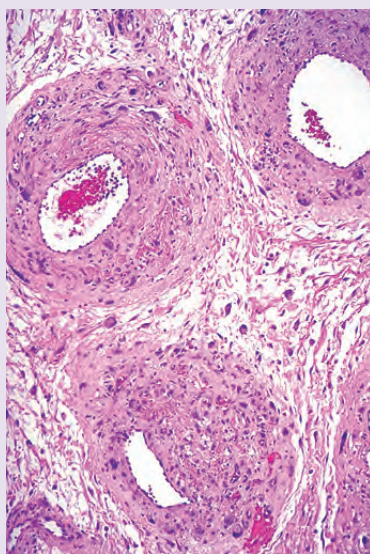
Recently Described Benign Vascular Tumors

Symplastic Hemangioma

Protuberant hemangioma with thrombosed vascular spaces



Atypical cells with bizarre hyperchromatic nuclei in the myoid cell wall of medium-sized veins, showing normal endothelia; inset: CD 34



Cl: Protuberant banal hemangioma.

Hi: Hemangioma with highly characteristic “ancient changes” within stroma and myoid cell wall, but not among the endothelia.

- Small hemangioma with dilated venules and medium-sized dermal veins
- Some of them thrombosed or with eosinophilic rims

- Regular endothelia without atypia and without mitoses; low proliferative activity
- Bizarre hyperchromatic stroma cells within the adjacent stroma
- No mitoses

DD: Angiosarcoma.

References

Goh, S.G., Dayrit, J.F., and Calonje, E. (2006) Symplastic hemangioma: report of two cases. *J Cutan Pathol* **33**(11): 735–40.

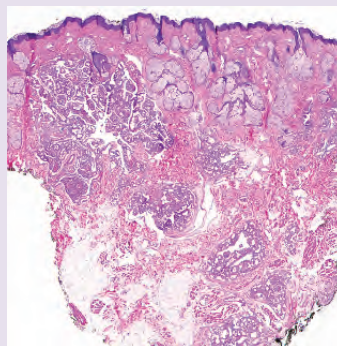
Kutzner, H., Winzer, M., and Mentzel, T. (2000) [Symplastic hemangioma] *Hautarzt* **51**(5): 327–31.

Papillary Hemangioma

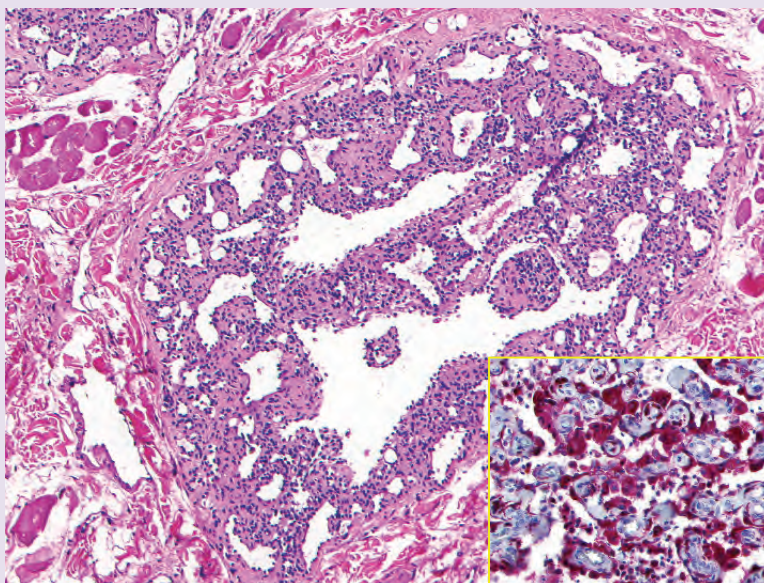
Bluish soft papules on the neck (left)



Sheets and tufts of aggregated capillaries (right)



Glomeruloid vascular spaces and capillary lobules



Inset: protuberant roundish endothelia, CD68 positive

Cl: Multiple papular solitary small hemangiomas.

Hi:

- Solid sheets and tufts of aggregated capillaries
- Small capillary lobules “free-floating” within glomeruloid vascular spaces
- Protuberant roundish endothelia with intracytoplasmic PAS-positive deposits
- PAS-positive endothelia express histiocytic markers CD68, CD163, and NKIC3

DD: Glomeruloid hemangioma; Kaposi's sarcoma; tufted hemangioma.

References

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Vascular Neoplasms of Intermediate Malignant Potential

This group of tumors mainly comprises the hemangioendotheliomas, i.e. Kaposi's sarcoma, papillary intralymphatic angioendothelioma, retiform hemangioendothelioma, pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma, and epithelioid hemangioendothelioma). Remarkably, recent reclassification subsumes epithelioid hemangioendothelioma under the classic angiosarcomas. Common clinical denominators of the hemangioendotheliomas are aggressive growth with common recurrences, rare metastases in local lymph nodes, but no lethal outcome.

The hemangioendotheliomas co-express endothelial markers (ERG, CD31) and podoplanin. There are important immunohistochemical hallmark markers: epithelioid hemangioendothelioma (CAMTA-1 or TFE-3) and epithelioid sarcoma-like hemangioendothelioma (FOS-B and AE1/AE3).

Kaposi's Sarcoma (KS)

Kaposi's sarcoma is a multisystem vascular neoplasm of low-grade malignancy, which is considered as a "vascular lesion of indeterminate or borderline status" by some authors. Its origin (blood or lymphatic vessels or pluripotent stem cells) and its definite reactive or neoplastic character are still issues of debate. From a clinical and etiological point of view, KS has to be differentiated into several categories: (1) classic KS; (2) endemic in sub-saharan Africans (adults and children); (3) iatrogenic immunodeficiency in transplant recipients due to immunosuppressive therapies or chronic renal failure; (4) epidemic HIV/AIDS-related KS, induced by human herpesvirus 8 (HHV 8) infection. The histological features are basically the same.

In the new WHO classification of skin tumors (2018), KS will be renamed as "HHV-8 associated vascular tumor."

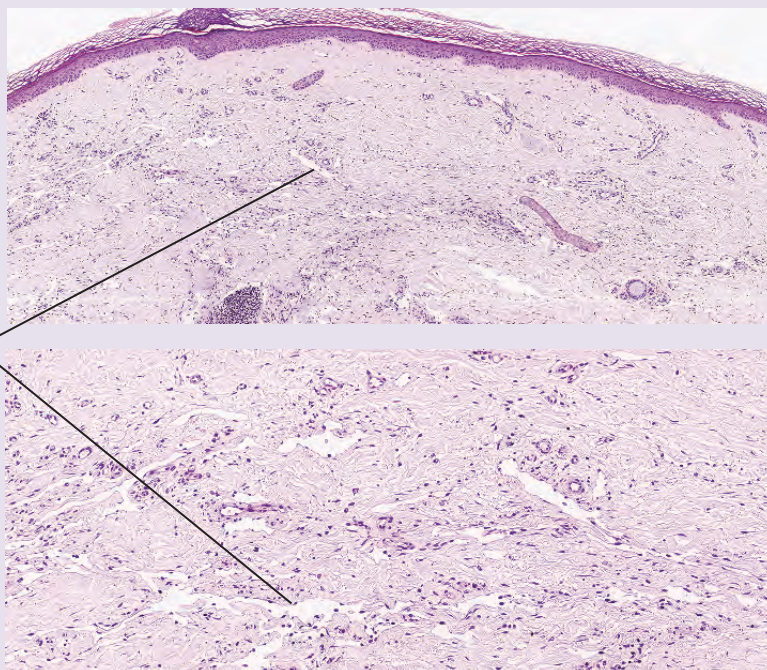
Kaposi's Sarcoma (Macular Stage)

Livid maculae
on both plantae



Kaposi's Sarcoma (Macular Stage)

Newly formed
markedly jagged
vascular spaces



Cl: In classic KS, there is a high prevalence of males, who are 15 times more often affected than females; most patients are Jews or Mediterranean Europeans.

The disease starts with blue-red or brown macules and lymphedema at the lower extremities, which slowly spread and after some months or even years transform into infiltrated plaques and nodules, which finally result in ulcerated, bleeding, and crusted tumorous lesions. Mucosal involvement is rare. Patients may die from involvement of liver or the gastrointestinal tract.

In KS associated with immunodeficiency (HIV/AIDS; immunosuppressive therapy; chronic renal failure), small red or blue-red firm papules and

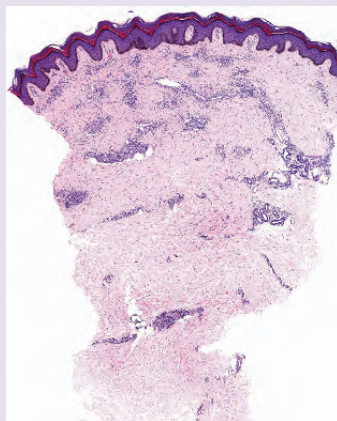
elongated nodules appear preferentially on the trunk along the skin lines and as blue patches in the mucosal areas.

Hi:

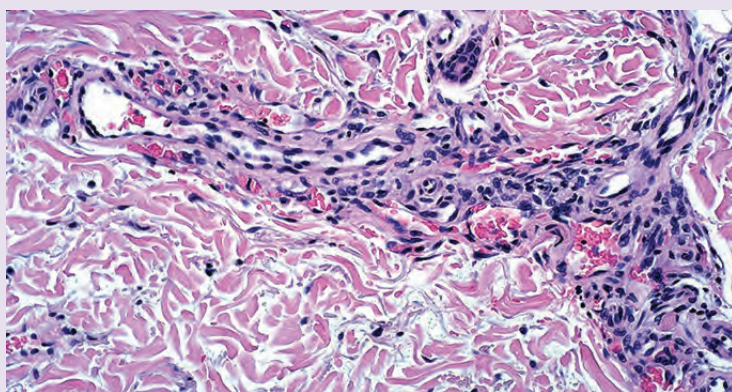
- Macular stage: the histological picture may be inconspicuous and almost normal
 - Stratum papillare uninvolved
 - Increased cellularity within the upper dermis
 - Irregular microvessels between collagen fibers lined by endothelium
 - Newly formed vessels protrude into vascular lumen or surround adnexal structures (promontory sign)
 - Focal accumulation of erythrocytes
 - Newly formed vascular spaces with HHV8- and podoplanin-positive endothelia

Kaposi's Sarcoma (Plaque Stage)

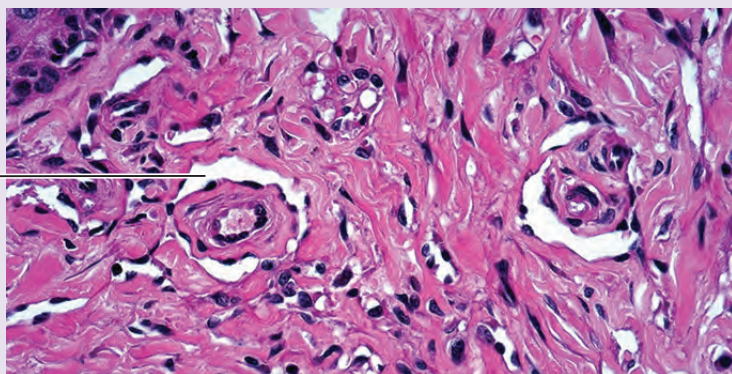
Blue-red plaques on the legs and feet



Vascular slits in conjunction with regular vessels (top right and mid)



Thin-walled vascular spaces surrounding pre-existing vessels ("promontory sign")



- Plaque stage:
 - Involvement of entire reticular dermis
 - Angulated irregular thin-walled small vascular lumina and slits adjacent to pre-existing vessels, adnexal structures, and between strands of collagen (promontory sign)
 - Dense proliferation of spindle cells (CD31+; CD34+; podoplanin+; HHV8+) arranged as fascicles
 - Mitotic activity
 - Hemorrhage with intra- and extravascular erythrocytes and hemosiderin and coin-like arrangement of erythrocytes

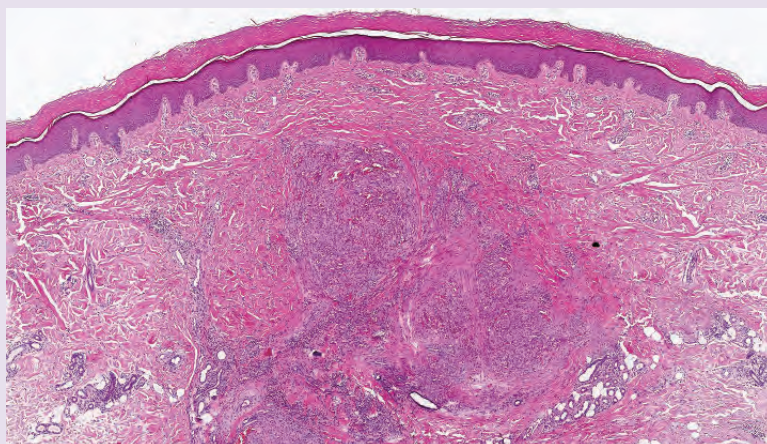
- Eosinophilic hyalin globules (PAS) (phagocytized red blood cells) in fusiform cells
- Fibrosis
- Inflammatory infiltrate containing plasma cells (pseudogranulomatous inflammatory pattern)

Kaposi's Sarcoma (Tumor Stage)

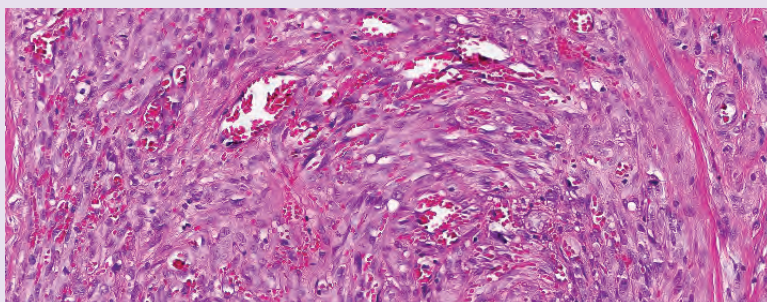
Multiple tumors of Kaposi sarcoma on the leg. Moulages (right)



Cellular richly vascularized tumor

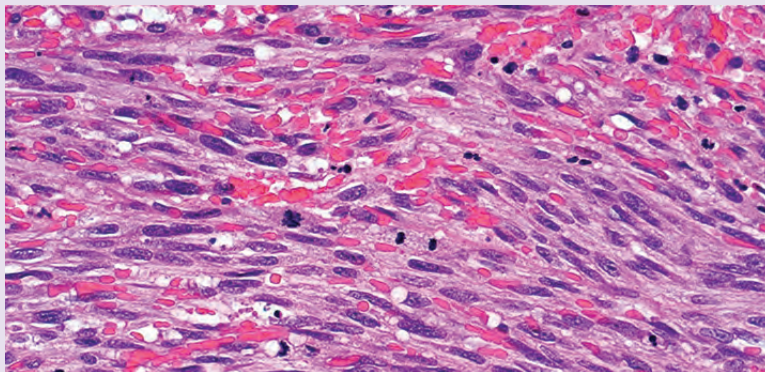


Dense proliferation of spindle cells. Thin vascular spaces filled with erythrocytes

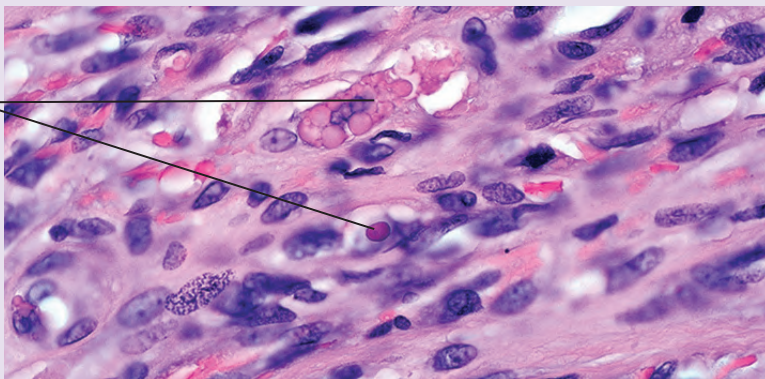


Kaposi's Sarcoma (Tumor Stage)

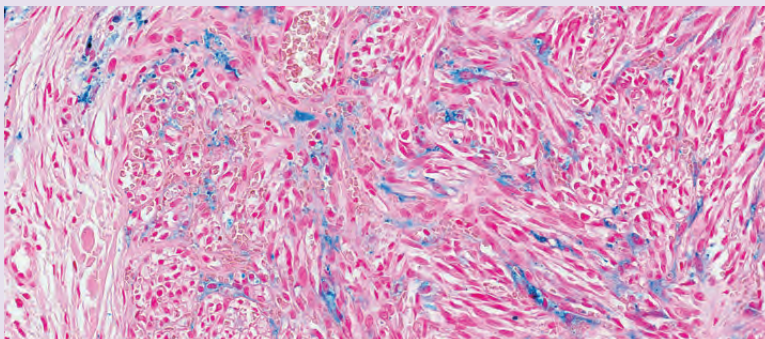
Dense proliferation of spindle cells. Thin vascular spaces filled with erythrocytes



Eosinophilic phagocytosed erythrocytes ("hyaline globi")



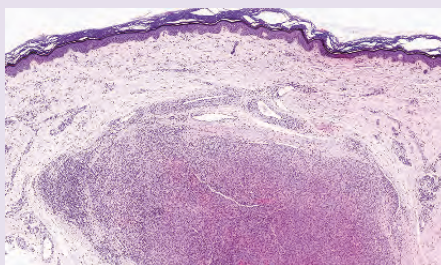
Characteristic hemosiderin deposits (Prussian blue)



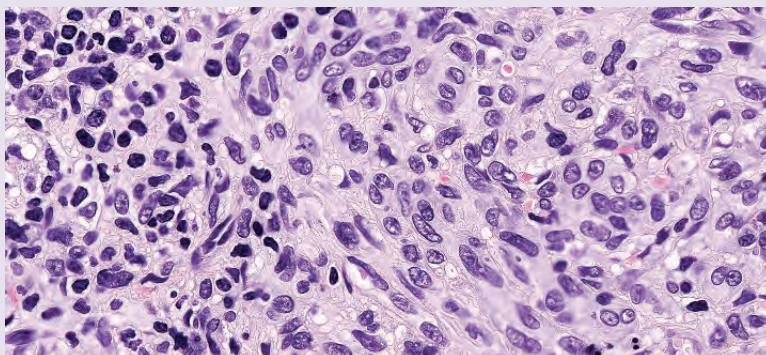
- Nodular/tumorous stage:
 - Exaggeration of the histological changes seen in plaque stage
 - Small vascular slits
 - Nodules of densely proliferating fusiform cells
 - Mitotic activity but no pleomorphism
 - Hyalin globules
 - Erythrophagocytosis

Kaposi's Sarcoma (AIDS Associated)

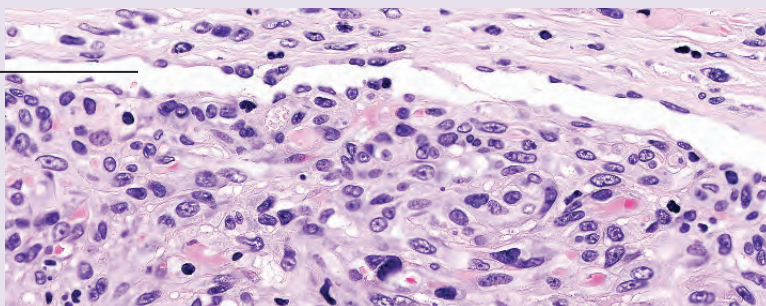
Typical brown-red papular and nodular lesions on the trunk in AIDS-related epidemic Kaposi sarcoma



Nodular proliferation of round and spindle cells showing little pleomorphism

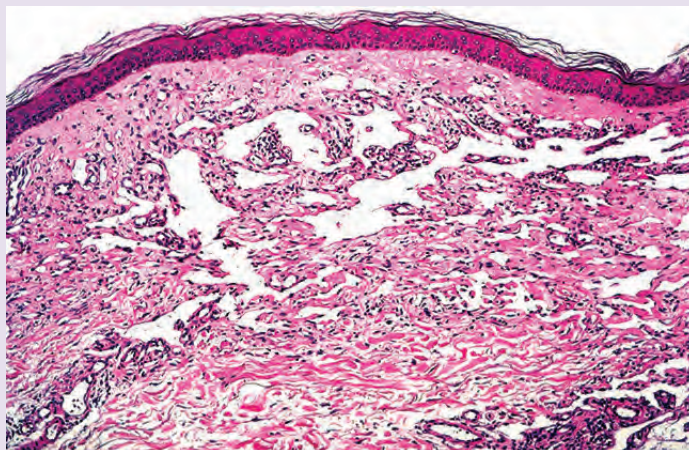


Thin-walled lymphatic spaces surrounding cellular infiltrate

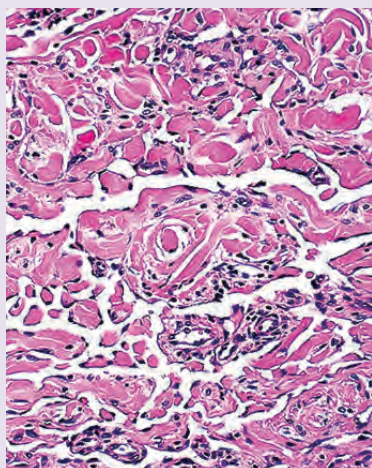


Kaposi's Sarcoma (Lymphangioma-Like Pattern)

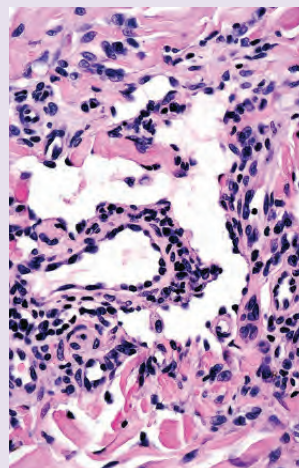
Bizarre lymphatic spaces in the upper and mid dermis closely reminiscent of progressive lymphangioma



Jagged vascular spaces amidst a dense collagenous stroma (left)



"Promontory sign" (right)



DD: Scar tissue; kaposiform hemangioendothelioma; hemangiosarcoma; dermatofibroma; acroangiodermatitis (pseudo-Kaposi); benign lymphangioendothelioma; leiomyoma; granuloma pyogenicum; bacillary angiomatosis; other spindle cell tumors; melanoma.

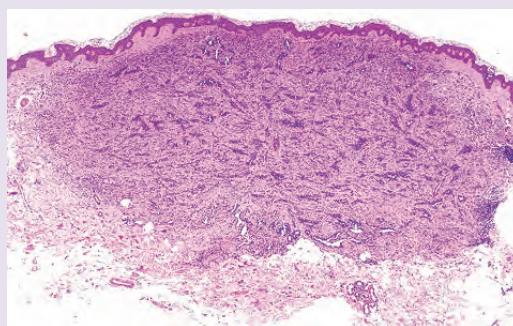
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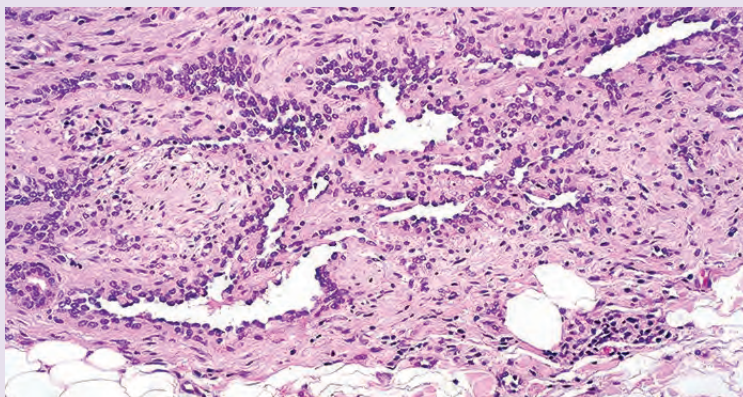
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Retiform Hemangioendothelioma

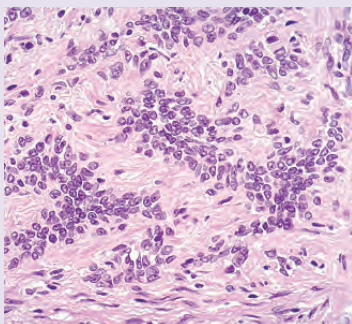
Plaques and nodules on the hand



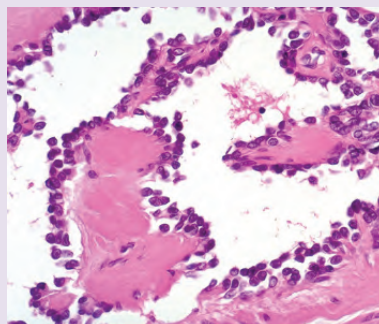
Retiform pattern of thin-walled vessels with protuberant hobnail endothelia (top right and mid)



Solid strands of hobnail endothelia (left)



Hobnail endothelia (right)



CI: Slowly growing, poorly demarcated plaque or nodule, occasionally hyperkeratotic, preferentially located on the extremities. Recurrences are common, metastases uncommon.

Hi:

- Circumscribed nodule in the reticular dermis and subcutis without sharp borders
- Labyrinth-like retiform vascular pattern
- Vertically oriented, branching and arborizing thin-walled vessels, forming bizarre vascular spaces
- Solid strands of proliferating endothelial cells
- Prominent (“lymphocyte-like”) endothelial cells protruding into vascular spaces (hobnail endothelia) (CD31+, CD34+, podoplanin+, HHV8 negative)
- Intravascular papillary projections
- Broad collagen bundles with hyalinization between vascular spaces
- Patchy lymphocytic infiltrate

DD: Papillary intralymphatic angioendothelioma; hobnail hemangioma; progressive lymphangioma; targetoid hemosiderotic hemangioma; radiation-induced angiosarcoma.

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Composite Hemangioendothelioma

CI: Rare solitary tumor on hands and feet of adults; other localisations have been reported.

Hi:

- Situated mainly within the deep dermis and the subcutaneous fat tissue
- Combination of various histological types of vascular tumors (benign, intermediate, and malignant) in the same lesion

References

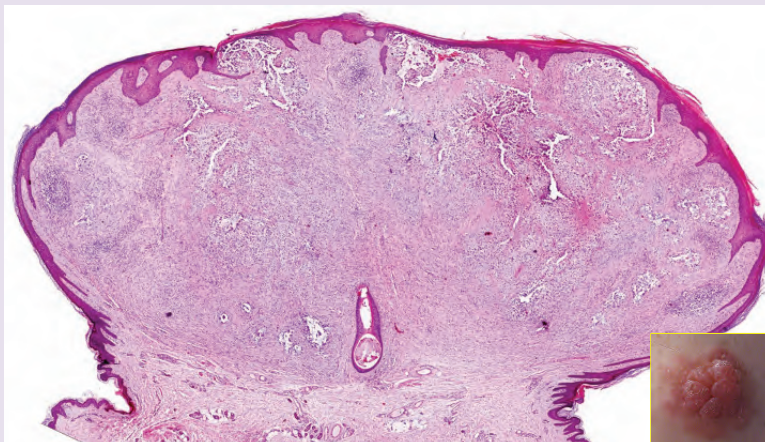
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Papillary Intralymphatic Angioendothelioma (PILA) (Malignant Endovascular Papillary Angioendothelioma (Dabska Tumor); Endovascular Papillary Hemangioendothelioma)

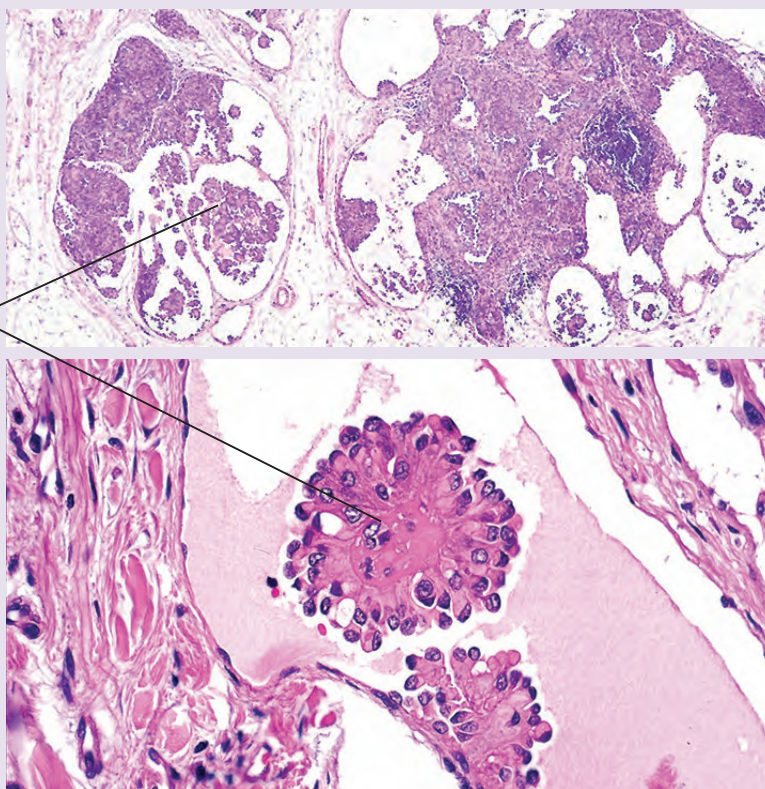
Malignant endovascular papillary angioendothelioma (Dabska tumor) is an exceedingly rare vascular proliferation of borderline malignancy. Histologically and probably also nosologically, it is identical with papillary intralymphatic angioendothelioma.

Malignant Endovascular Papillary Angioendothelioma (Dabska Tumor)

Lobular dermal tumor with dilated and jagged lymphatic spaces. Inset: papillary lesion on the leg



Dilated lymphatic spaces with intraluminal papillae and tufts of densely packed hobnail endothelia sitting on collagenous cores



CI: Locally aggressive growing dermal tumor occurring in children and adults. No metastases.

Hi:

- Compact sheets and dilated vascular spaces, expressing lymphatic endothelial markers (podoplanin)
- Monomorphous epithelioid or “large lymphocyte-like” hobnail endothelia
- Intraluminal papillary projections with collagenous cores and aggregated hobnail endothelia on the surface (“Dabskoid tufts”)

DD: Lymphangioma circumscriptum; retiform hemangioendothelioma.

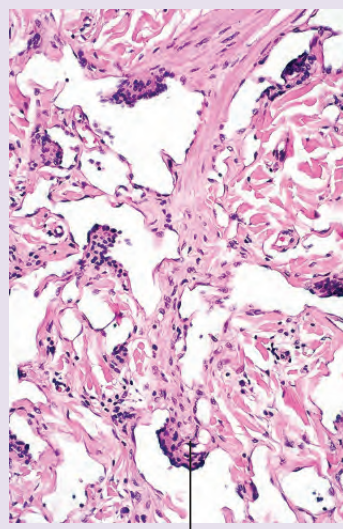
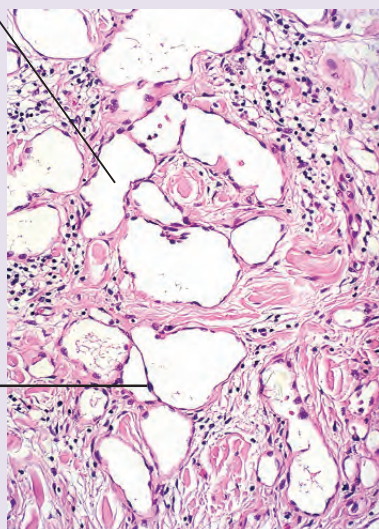
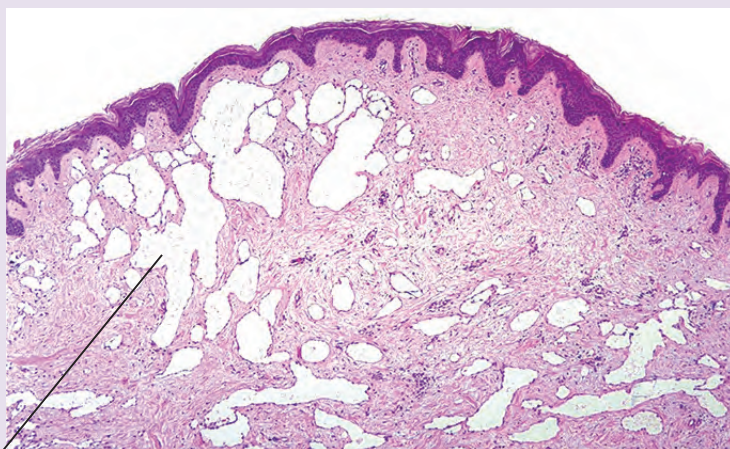
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Radiation-Induced Atypical Vascular Lesion (AVL) (Benign Lymphangiomatous Papule (BLAP))

Dilated lymphatic vessels of various sizes and shapes with regular endothelia

Back-to-back arrangement of lymphatic vessels



Intraluminal “Dabskoid tufts” of hobnail endothelial cells

Atypical vascular lesions (AVL) after radiotherapy (syn: benign lymphangiomatous papules (BLAP)) present with an almost identical clinicopathological setting. Their role as precursor lesion of angiosarcoma is still a matter of debate. Histopathological differentiation from incipient angiosarcoma may be cumbersome without cytogenetic (FISH) and immunohistochemical methods. Remarkably, AVL/BLAP are clearly negative for MYC expression and MYC amplification; there is no significant proliferative activity ($Ki67 < 5\%$).

Cl: Small red papular or plaque-like vascular lesions, mostly in women after radiation therapy for breast or ovarian cancer.

Hi:

- Lacuna-like wide and slit-like thin-walled vascular spaces in the dermis
- Increased number of small thin-walled vessels with slightly hyperchromatic endothelia
- Small endothelia with little pleomorphism

- Endothelia express the lymphatic marker podoplanin
- Projections with plump hobnail endothelia into the vascular lumina

DD: Lymphangiomatosis; incipient angiosarcoma.

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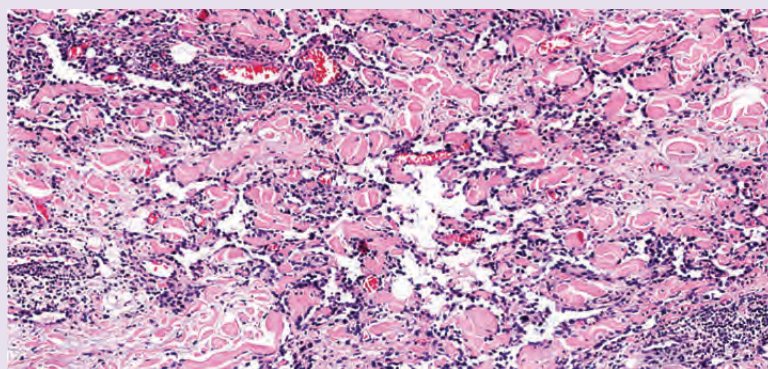
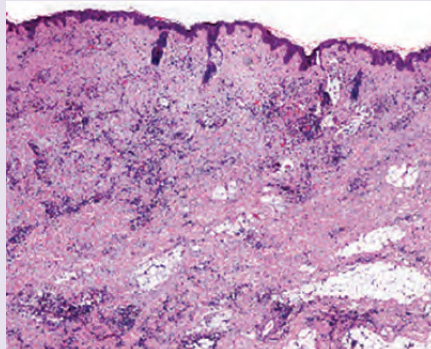
Vascular Neoplasms with High Malignant Potential

Cutaneous Angiosarcoma

Bruise-like lesion on the forehead (left)



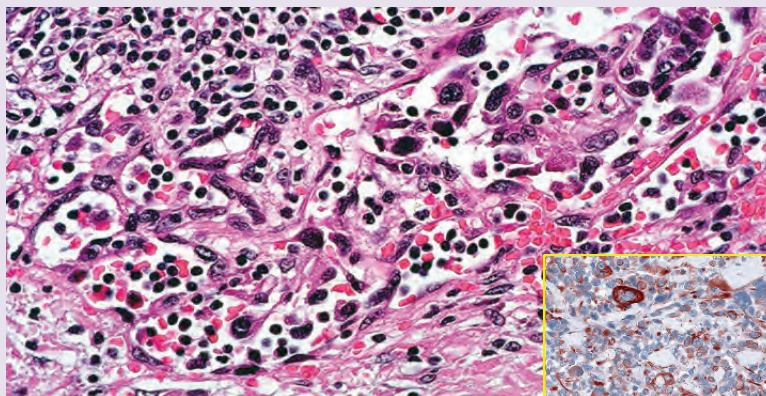
Bizarre arborising slits and vascular spaces with markedly atypical endothelial tumor cells (top right and bottom)



Cutaneous Angiosarcoma

Pleomorphic and hyperchromatic atypical endothelial tumor cells lining atypical vascular spaces

Inset: CD31



The skin is the most common organ affected by this highly malignant tumor of blood or lymphatic vessels, which also can develop in various visceral organs and bone and which has a very poor prognosis.

Cl: Angiosarcoma of the skin can appear in various clinical settings, usually with ill-defined borders.

- Spontaneously on the head of elderly people. Angiosarcomas present as macular or plaque-like red or violaceous bruise-like slowly growing lesions, often imitating inflammatory facial dermatoses (e.g. “unilateral” rosacea or erysipelas). Later, infiltrated plaques, nodules, tumors and ulceration occur
- Secondary to chronic lymphedema of the limbs (Stewart–Treves), and following mastectomy
- Dermal tumors, following ionizing irradiation or after trauma and ulceration

Hi:

- Epidermis normal or atrophic
- Infiltrative growth pattern
- Atypical endothelial tumor cells with marked pleomorphism
- Many mitoses
- Intraluminal multilayering (“piling up”) of atypical endothelia
- Tumor cells positive for endothelial markers ERG and CD31, often co-expressing podoplanin and myc

- Multiple histological variants. The most common are:

- Angiomatous: irregular bizarre vascular channels, with jagged spaces, slits, and lacunae throughout the dermis, dissecting collagen bundles
- Spindle cell variant
- Granular cell and foamy cell variant
- Anaplastic variant with atypical pleomorphic endothelial cells
- Erythrocytes intra- and extravascular (“bloody dermis”)

Immunohistochemistry: Remarkably, cytokeratins may be focally expressed.

DD: Kaposi’s sarcoma; epithelioid angiosarcoma; epithelioid hemangioendothelioma; hemangiopericytoma; pseudoangiosarcomatous carcinoma; acantholytic squamous cell carcinoma; Indian file metastasis of adenocarcinoma or malignant melanoma; pyogenic granuloma; dermatofibroma.

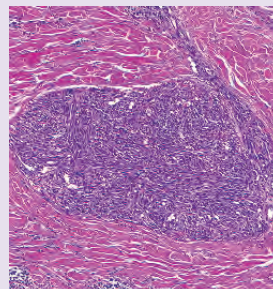
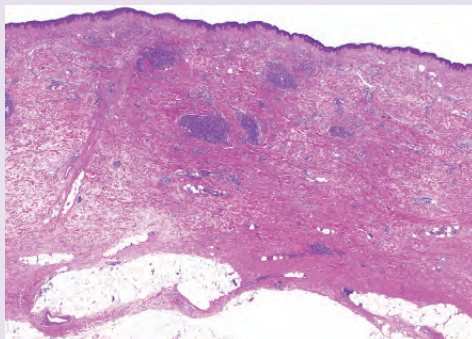
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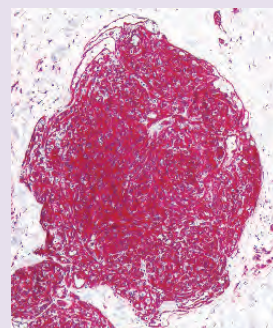
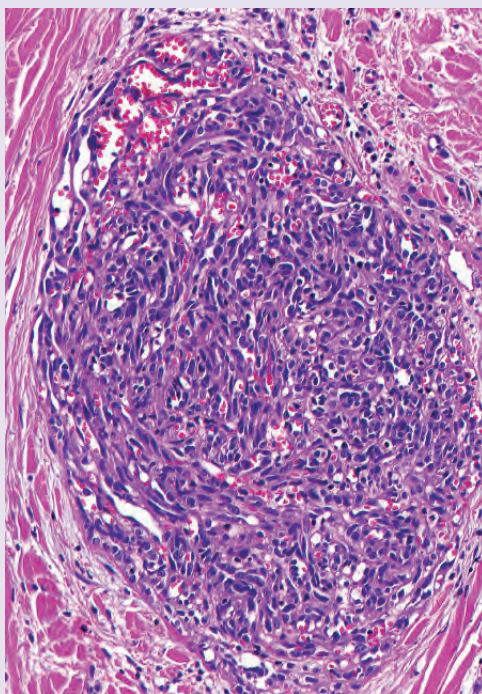
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Radiation-Induced (Postradiation) Angiosarcoma

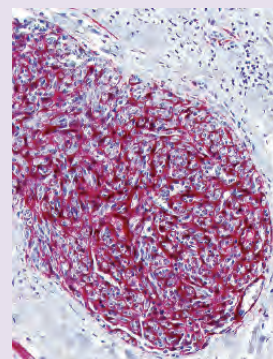
Foci of dermal infiltrates



Mostly spindle-shaped atypical cells and slit-like spaces with intraluminal and extraluminal red blood cells (left)



CD31 (upper right) and ASMA-positivity (bottom right)



Cl: Solitary or multiple papular blue-black skin lesions.

Hi:

- Epidermis not affected
- Solid epithelioid or solid spindle cell foci in the dermis
- Slit-like spaces, containing intraluminal or extravasated erythrocytes
- Importantly, endothelia co-express podoplanin and myc, with concomitant high (>10%) proliferative activity (Ki67)
- *MYC* gene amplification (FISH)

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Epithelioid Hemangioendothelioma

Due to its aggressive course, epithelioid hemangioendothelioma has been subsumed under the

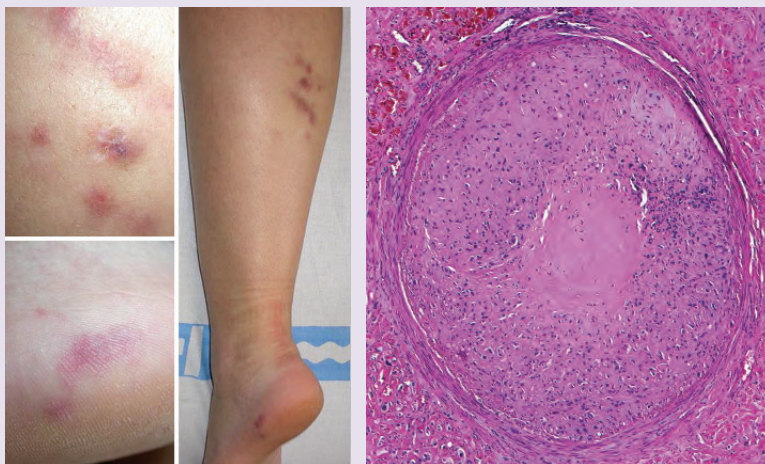
angiosarcomas. Together with epithelioid angiosarcoma, it represents the malignant end of the

spectrum of epithelioid vascular tumors. They metastasize early and have a poor prognosis.

Epithelioid Hemangioendothelioma

Red dermal nodules on the leg (left)

Angiocentric infiltrate (right)



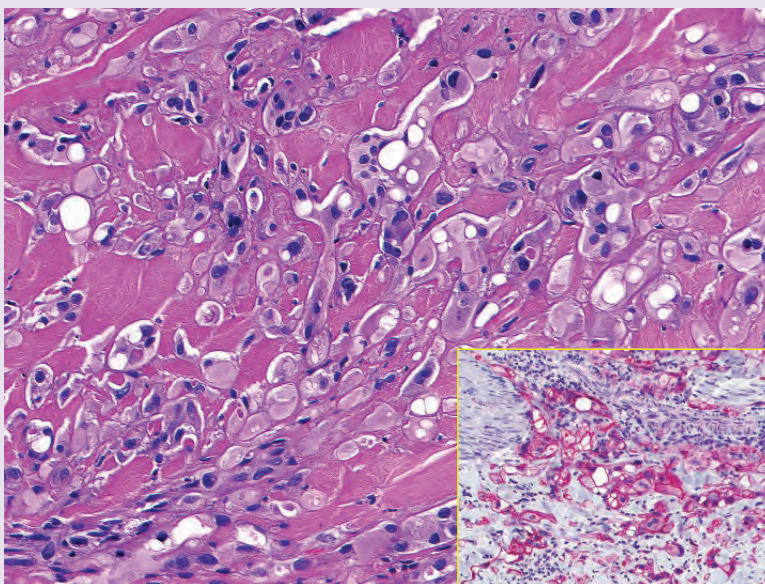
CI: Involvement of various organs and occasionally presenting in the skin, showing solitary or

multiple cutaneous plaques or nodules, preferentially involving the extremities.

Epithelioid Hemangioendothelioma

Cords of plump epithelioid endothelial cells with vacuoles ("blister cells") in a hyalinized fibrous stroma (left)

Podoplanin positive epithelioid cells (inset)



Hi:

- Angiocentric, multifocal neoplasm
- Nodules and sheets of large polygonal epithelioid cells with abundant eosinophilic cytoplasm and large nuclei with large nucleoli (CD31+, ERG+, vimentin+, epithelial membrane antigen (EMA) and cytokeratins variably expressed)
- Intracytoplasmic vacuoles (“blister cells”)
- Few vascular spaces, sometimes with jagged contours
- Mitoses, pyknotoses, necroses

Immunohistochemistry: Importantly, epithelioid angiosarcoma does not express hallmark markers of look-alike tumors with epithelioid endothelia: epithelioid hemangioma (FOS-B), epithelioid hemangioendothelioma (CAMTA-1 or TFE-3), epithelioid-sarcoma like hemangioendothelioma (FOS-B and AE1/AE3).

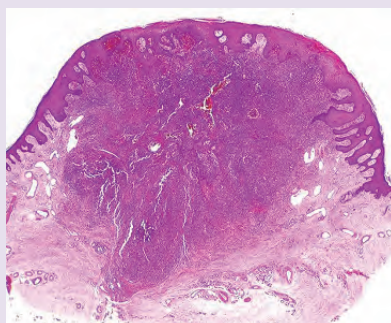
DD: Epithelioid hemangioma; metastasizing squamous cell carcinoma; metastasizing malignant melanoma; granulomatous or infectious lesions.

References

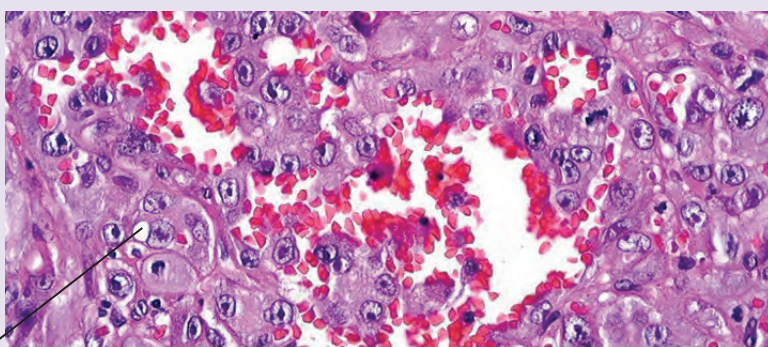
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Epithelioid Angiosarcoma

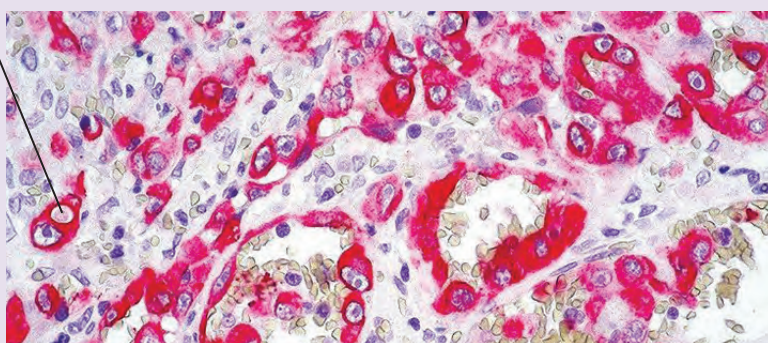
Nodular tumor



Large atypical epithelioid tumor cells surrounding jagged vascular spaces



Large CD31 positive tumor cells with intracytoplasmic vacuoles



Cl: Most aggressive vascular tumor, which metastasizes early and has a poor prognosis.

Hi:

- Epithelioid endothelial cells protruding into vascular spaces
- Significant cytological atypia and mitotic activity
- Intracytoplasmic vacuoles
- Dissection of collagen bundles by tumor cells

Immunocytochemistry: Pan-cytokeratin expression within endothelial cells is not uncommon and can lead to confusion in differential diagnosis with an acantholytic squamous cell carcinoma.

DD: Poorly differentiated carcinoma or melanoma.

References

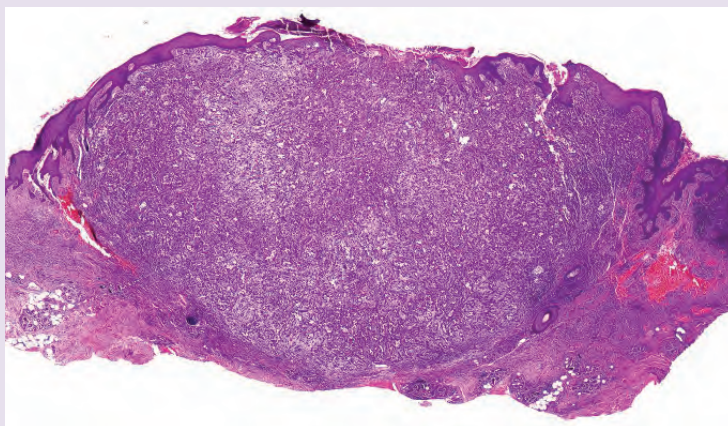
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Differential Diagnosis: Acantholytic (Angiosarcoma-Like) Squamous Cell Carcinoma

See also acantholytic squamous cell carcinoma (epithelioma spinocellulare segregans Delacretaz Chapter 1)

Differential Diagnosis: Acantholytic (Angiosarcoma-Like) Squamous Cell Carcinoma

Circumscribed tumor, originating from the ulcerated epidermis, extending throughout the dermis

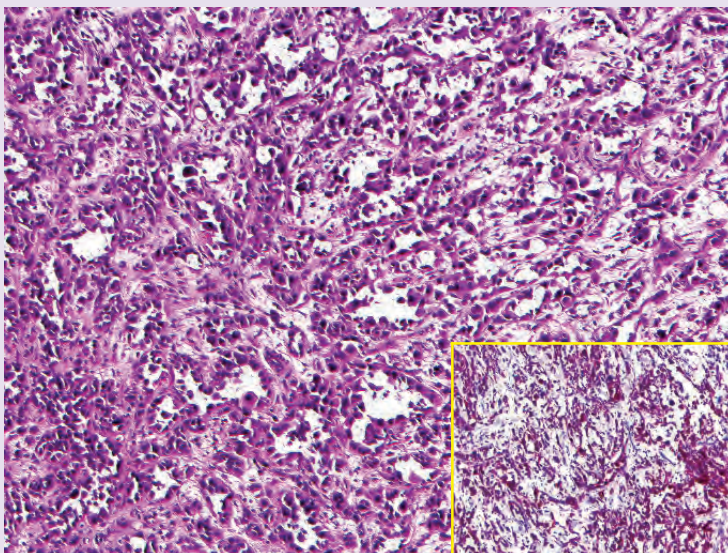


CI: Exo- or endophytic tumor with criteria of squamous cell carcinoma.

Differential Diagnosis: Acantholytic (Angiosarcoma-Like) Squamous Cell Carcinoma

Acantholytic squamous cells, simulating angiomatous slits and lacunae

Inset: tumor cells express cytokeratin (CK4)



Hi:

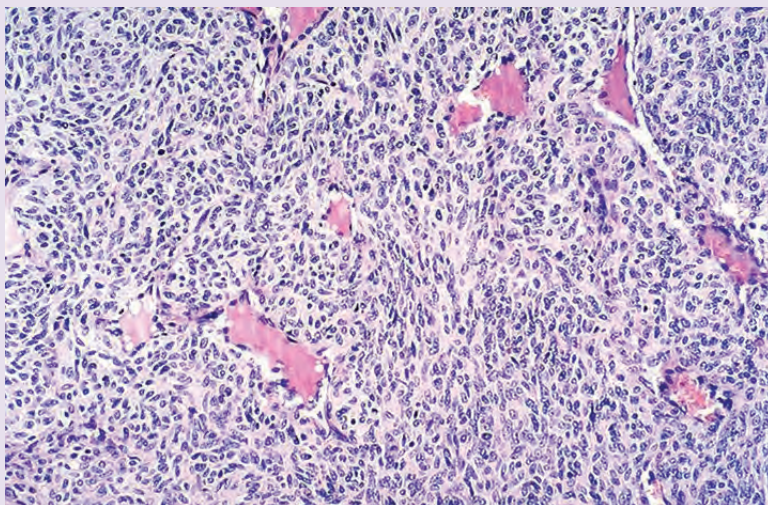
- Squamous cell carcinoma with large atypical keratinocytes and a conspicuous dyscohesive tumor pattern (“neoplastic acantholysis”)
- Simulation of angiomatous slits and lacunae

Immunophenotype: Expression of cytokeratins. Negative for endothelial markers.

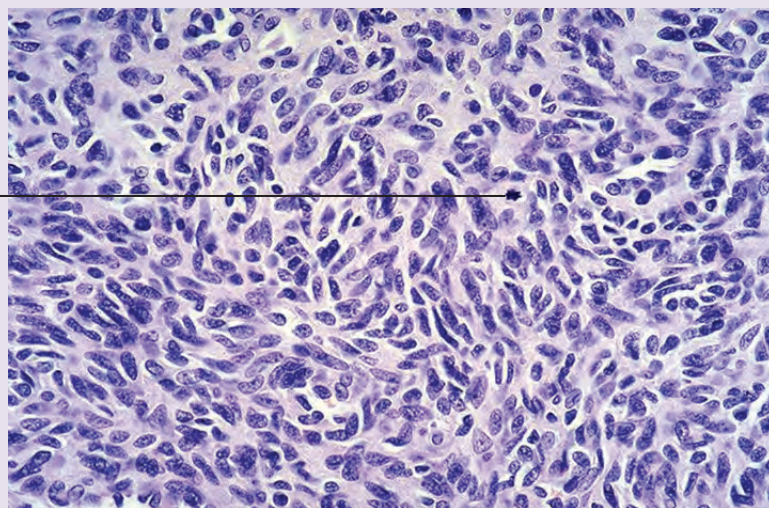
DD: Epithelioid angiosarcoma; epithelioid heman-gioendothelioma.

Glomangiosarcoma (Malignant Glomus Tumor)

Malignant
glomus tumor
with sheets
of atypical
glomus cells



Atypical glomus
cells and multiple
mitoses



Cl: Rare malignant transformation of glomus tumor.

Hi: Areas of classic glomangioma gradually blending into zones with pleomorphic tumor

cells and mitoses. Most glomangiosarcomas present as homogeneous highly pleomorphic tumors with a desmin-negative and alpha-SMA-positive immunophenotype. Many mitoses.

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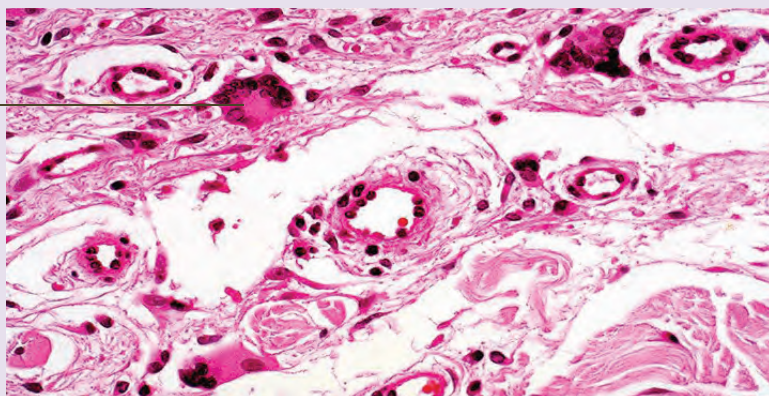
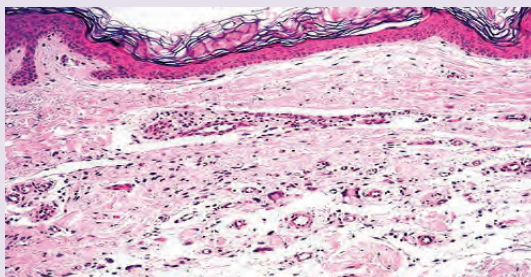
Other Neoplasms with Significant Vascular Component

Multinucleate Angiohistiocytoma

Multiple red-brown papules (left)

Increased number of capillaries and small venules (right)

Multinucleated giant cells



Cl: Solitary or multiple brownish nodules and small plaques, preferentially on the dorsa of hands, feet, and on the knee. Facial lesions are not uncommon.

Hi:

- At scanning magnification, close resemblance to richly vascularized dermatofibroma
- Dense stroma

- Increased number of capillaries and venules
- Interspersed multinucleated giant cells

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Angiofibroma (Adenoma Sebaceum Associated with Pringle–Bourneville Disease)

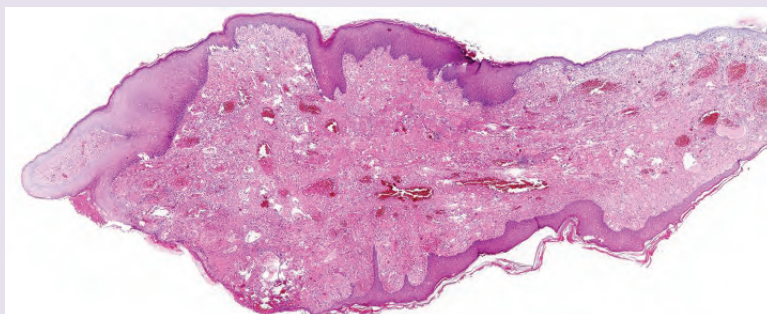
This particular variant of the angiofibromas represents the cutaneous manifestation of tuberous sclerosis (Pringle–Bourneville disease).

Angiofibroma

Multiple dense firm papules on the face and at the nasolabial fold (left). Moulage (right)



Fibrous nodule with dilated vessels

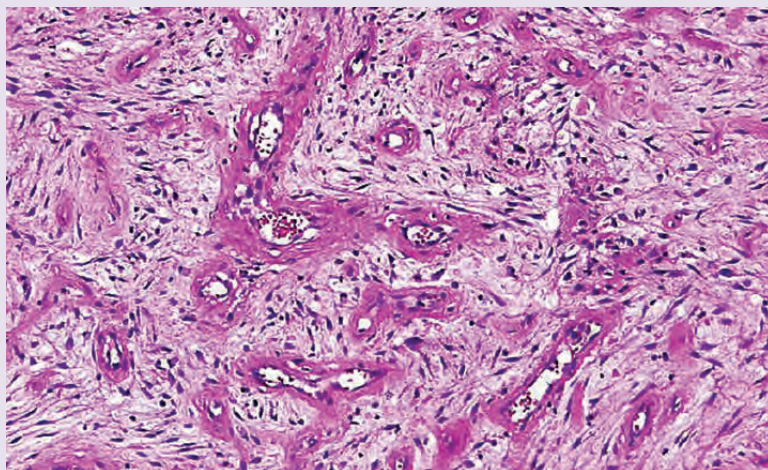


CI: Preferentially the nasolabial fold and the cheeks, but also other facial and extrafacial localisations are involved. Multiple tiny pink or

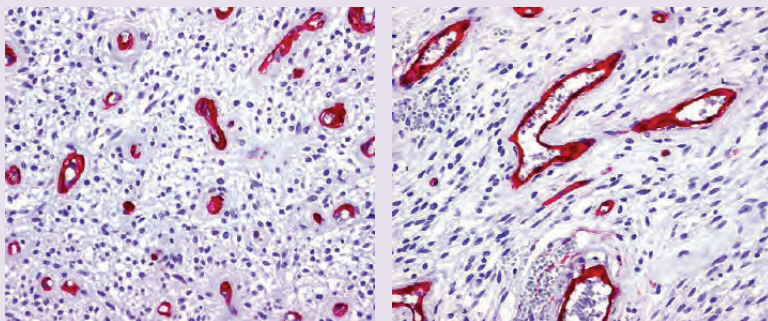
skin-colored papules; pink periungual tumors, typically on lower extremities; other organs involved: CNS, eyes, bones, inner organs (phacomatosis).

Angiofibroma

Dilated venules
with fibrotic
stroma



CD31 stain
of regular
endothelia

**Hi:**

- Increased swirly collagen fibers
- Increased number of thick-walled dilated blood vessels
- Stellate fibroblasts
- Atrophic sebaceous glands

DD: Trichoepitheliomas; cylindromas; rosacea; dermal nevi; angiofibroma of the nose (fibrous papule of the nose).

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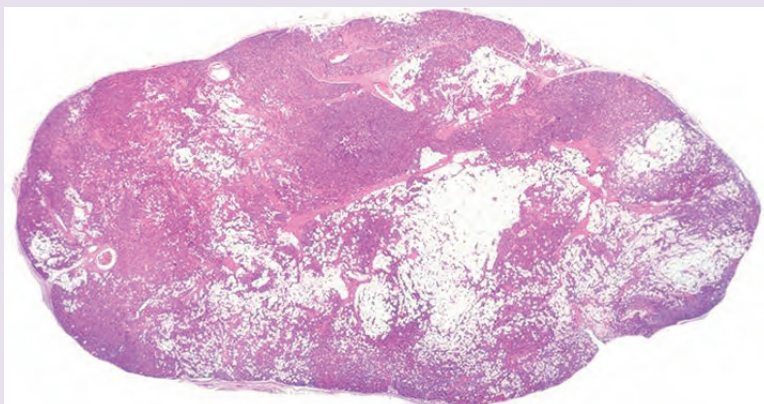
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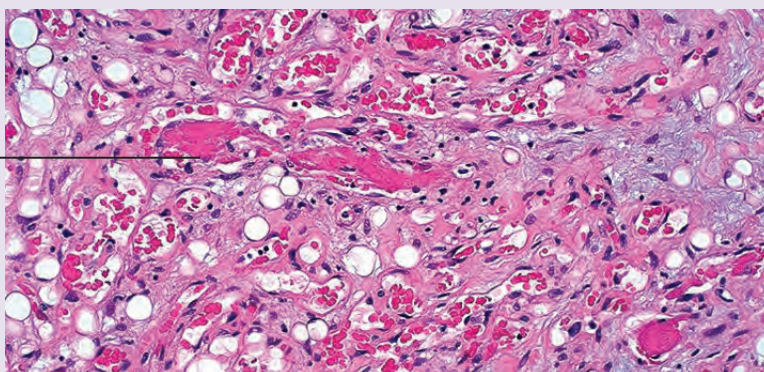
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Angiolipoma

Lobular fat with an abundance of thin-walled venules



Characteristic platelet-rich thrombi



Richly vascularized lipoma. Recent findings suggest that angiolipoma is an acquired hemangioma variant with predilection of the lobular subcutaneous fat

Cl: Painful subcutaneous nodule. Often multiple and acquired.

Hi:

- Sharply demarcated subcutaneous nodule with thin pseudocapsule
- Diffuse proliferation of small venules and rare capillaries within the subcutaneous fat
- Cellular variant: vessels may coalesce to large intralobular sheets
- Hallmarks are eosinophilic CD61-positive platelet thrombi within some or all of the vessels

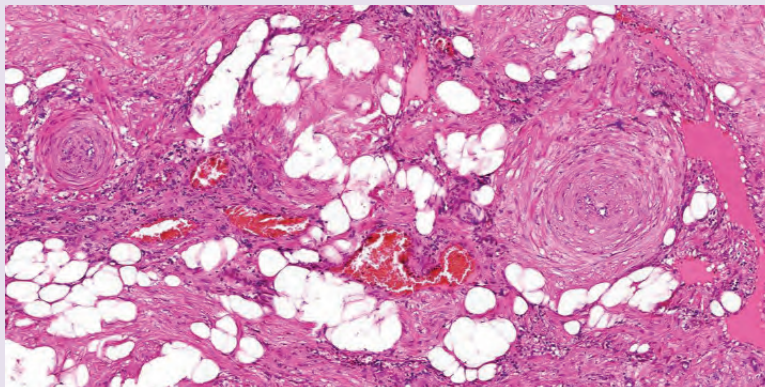
DD: Lipoma; hemangioma; angiolipoma; Kaposi's sarcoma.

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Angiolipoleiomyoma (Angiomyolipoma)

Combination of fatty tissue, smooth muscle bundles, and thick-walled venules ("angiolipoleiomyoma")



Cl: Benign tumor, most likely angioleiomyoma variant with accompanying (metaplastic) fat. Renal angiomyolipoma with strong expression of HMB-45 may be associated with Birt–Hogg–Dubé syndrome.

Hi: Sharply circumscribed combined proliferation of blood vessels, smooth muscle, and fat.

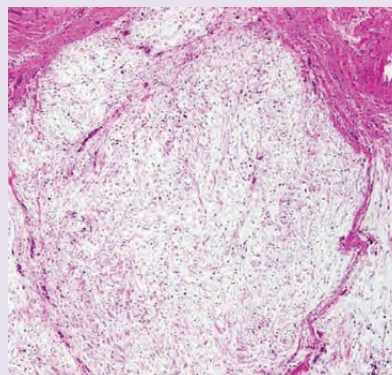
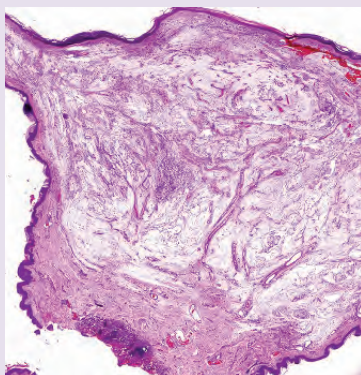
DD: Cellular angiolipoma.

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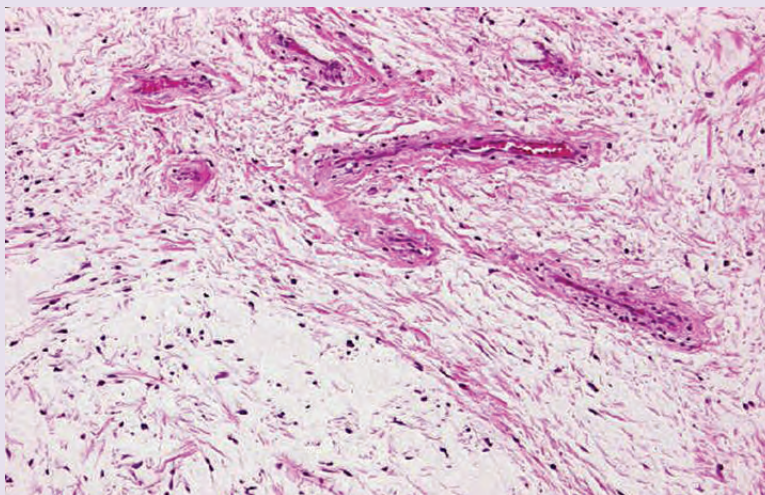
Angiomyxoma

Mucinous stroma and delicate vessels in the dermis

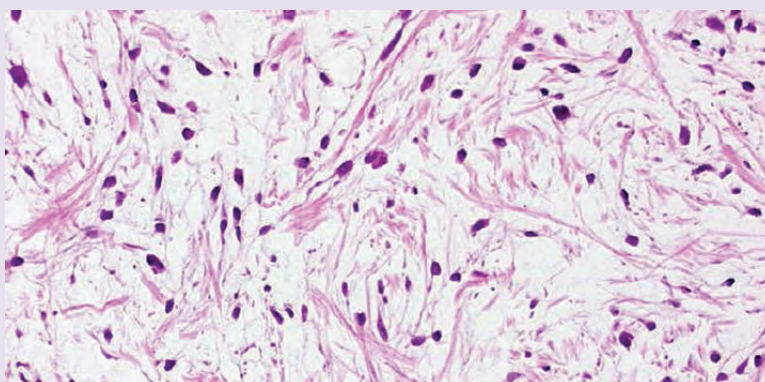


Angiomyxoma

Small venules



Spindled fibroblasts and scant neutrophils



Cl: Small nodule resembling a cyst.

Hi:

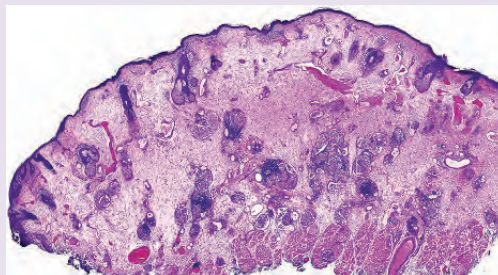
- Mucinous stroma in the dermis and subcutis with prominent vessels
- Spindled and stellate fibroblasts
- Mast cells and neutrophilic granulocytes (“sprinkle of neutrophils”)

References

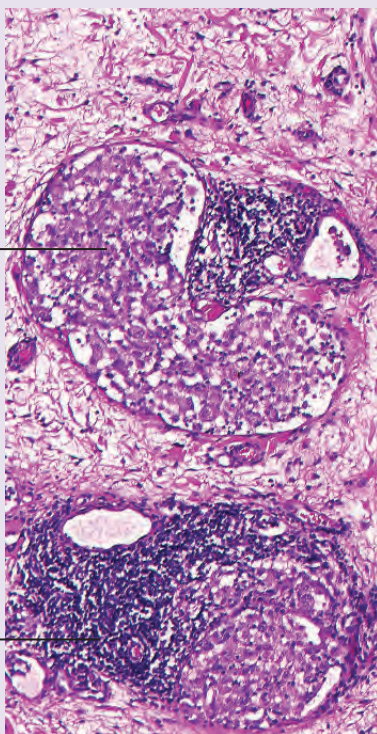
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Intralymphatic Histiocytosis

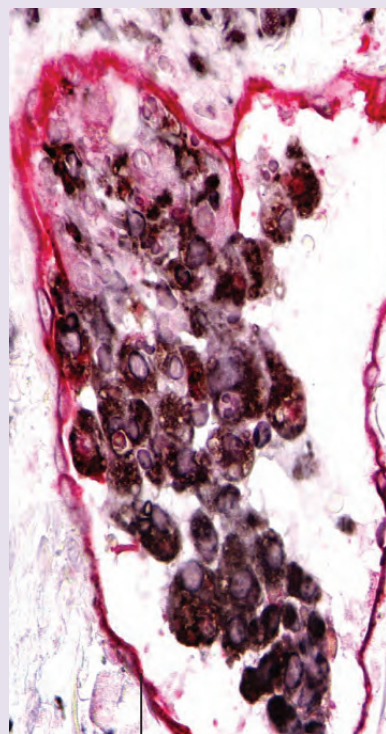
Diffuse tumorous swelling of the cheek and eyebrows (left) due to nodular infiltrates in the dermis, edema and fibrosis (right)



Intralymphatic histiocytes; CD68 positive (right)



Inflammatory lymphocytic infiltrate



Lymph vessels; CD31 positive

Cl: Erythemas or flat erythematous plaques, sometimes with nodular surface. Often in association with underlying endoprosthesis (hip, knee).

Hi:

- Dilated thin-walled lymphatic vessels in all levels of the dermis
- Podoplanin-positive endothelia
- Dense aggregates of intraluminal histiocytic cells (CD14+, CD68+, CD163+)
- Perivascular mixed infiltrate composed of lymphocytes, plasma cells, histiocytes, and granulocytes

- Importantly, endothelial marker CD31 may be misleading due to its cross-reactivity with histiocytes

DD: Intravascular lymphomatosis (intravascular T- or B-cell lymphoma, intravascular malignant histiocytosis); reactive angioendotheliomatosis.

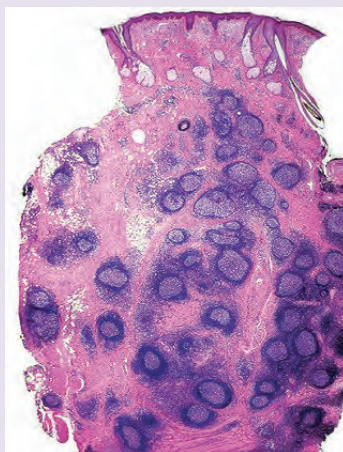
Reference

Takiwaki, H., Adachi, A., Kohno, H., and Ogawa, Y. (2004) Intravascular or intralymphatic histiocytosis associated with rheumatoid arthritis: a report of 4 cases. *J Am Acad Dermatol* 50(4): 585–90.

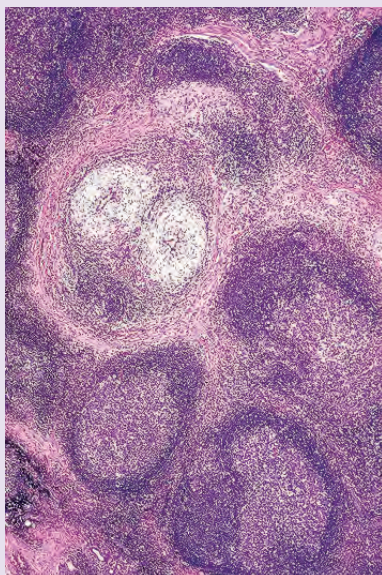
Kimura's Disease

Subcutaneous swelling on the forehead (left)

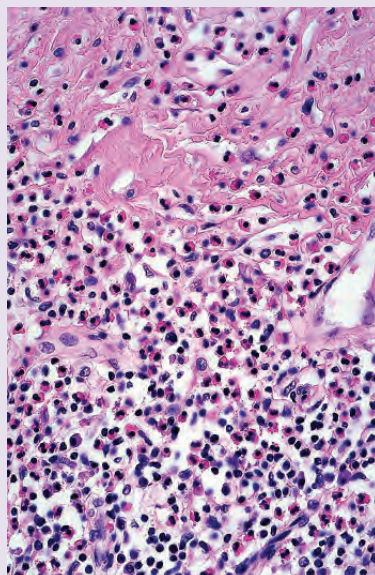
Lymphoid follicles in the dermis and subcutis (right)



Lymph follicles with germinal center formation. Thick-walled vessels with enlarged endothelia (left)



Lymphocytic infiltrate rich with eosinophils (right)



Courtesy of L Requena, Madrid

Kimura's disease occurs as an immune-reactive lymphocytic condition in Asian individuals. The skin is rarely involved. It is not a vascular tumor and does not belong to the family of epithelioid vascular tumors.

Cl: Subcutaneous swelling, preferentially in the parotid and submandibular regions of young adult males, associated with marked lymphadenopathy,

blood eosinophilia, and increased serum levels of immunoglobulin (IgE).

Hi:

- Dense lymphocytic infiltrate with admixture of eosinophils
- Dilated blood vessels
- Prominent lymphoid follicles with germinal center formation

- Tissue eosinophilia
- No epithelioid endothelial cells
- Septal fibrosis

DD: Epithelioid hemangioma; cutaneous B-cell lymphomas (marginal zone and follicle center lymphoma); pseudolymphoma; bacillary angiomatosis; epithelioid angiosarcoma.

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CHAPTER 7

Fat

CHAPTER MENU

Nevus (Hamartoma)	Benign Neoplasms
Nevus Lipomatosus Superficialis Hoffmann Zurhelle	Malignant Neoplasms
Neoplasms of Fat Tissue	

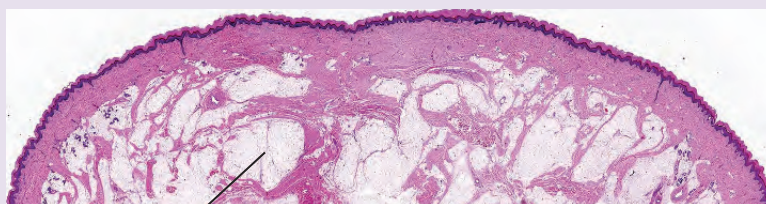
Nevus (Hamartoma)

Nevus Lipomatosus Superficialis Hoffmann Zurhelle

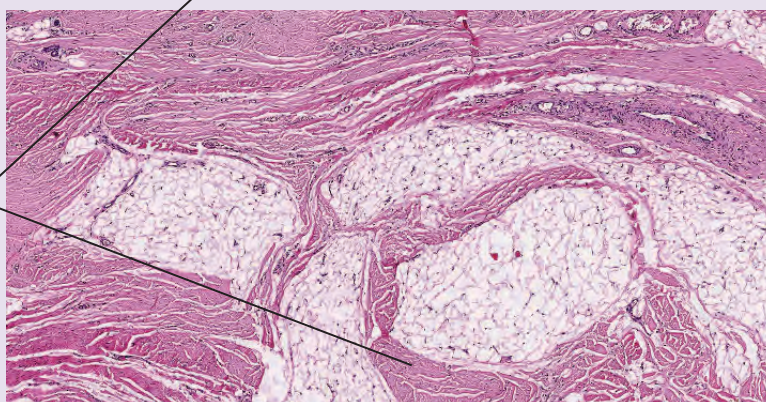
Groups of yellow soft nodules on the buttock (left) and the leg (right)



Fatty tissue reaching into the mid and upper dermis



Lobular fatty tissue of different sizes and shapes. Wide collagenous septa.



Cl: Soft yellowish papules and nodules, single or in groups or in linear arrangement, on the buttocks and thighs but also in other areas, frequently unilateral. The surface may be wrinkled or cobblestone-like. Lesions are present at birth or appear during infancy.

Hi:

- Thinned dermis
- Multiple lobules of normal fat in the mid- and deep dermis, usually sparing the papillary dermis

- Fibrotic septa

DD: Focal dermal hypoplasia; myxoma; clinically, neurofibroma, melanocytic nevi.

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BENIGN NEOPLASMS

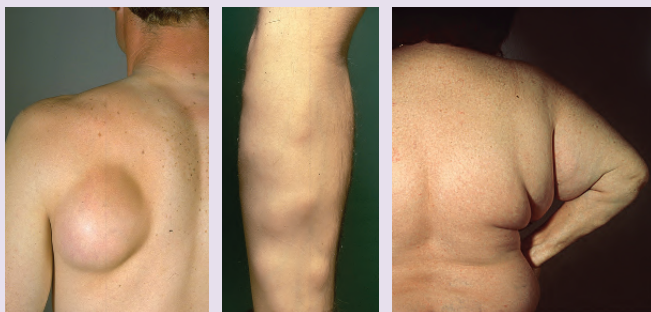
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Neoplasms of Fat Tissue

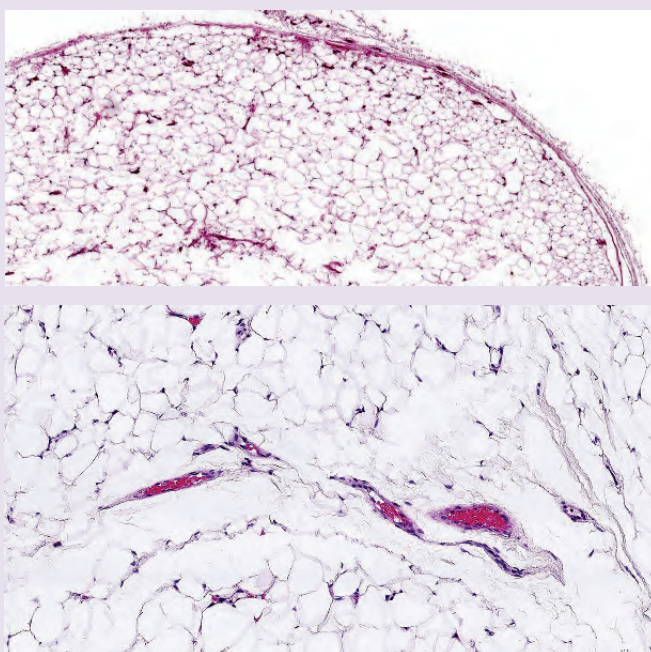
Benign Neoplasms

Common Lipoma and Lipomatosis

Solitary (left), multiple (mid) lipomas and diffuse lipomatosis (Launois-Bensaude) (right)



Mature adipose tissue (mid and bottom)



BENIGN NEOPLASMS

Cl: Poorly defined subcutaneous soft nodules or tumors, single, multiple or diffuse (Launois–Bensaude syndrome). Rarely painful, except when impinging on nerves.

Hi:

- Large lobules of mature adipose tissue
- Regular adipocytes
- No lipoblasts
- Rarely large macrophages (“pseudolipoblasts”) – particularly in post-traumatic lesions

Immunohistochemistry: Negative for MDM2 and CDK2.

DD: Deep neurofibroma; cyst; any subcutaneous tumor.

References

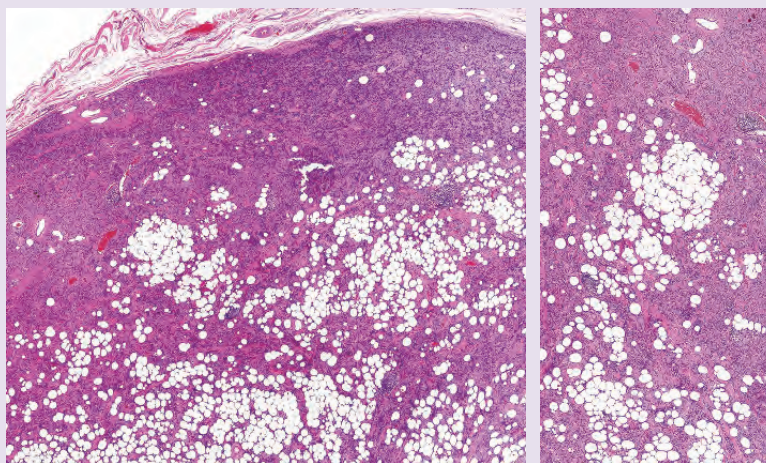
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Angiolipoma (see Vessels, Chapter 6)

Angiomyolipoma (see Vessels, Chapter 6)

Spindle Cell Lipoma

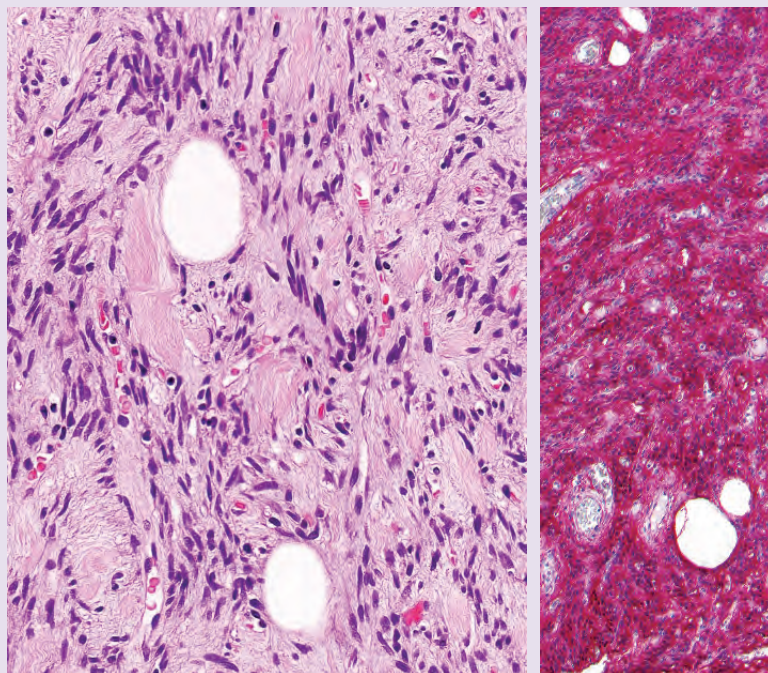
Sharply circumscribed spindle cell tumor with interspersed clusters of lipocytes



BENIGN NEOPLASMS

Spindle Cell Lipoma

Solid proliferation of spindle cells entrapping lipocytes (left). CD34 positive spindle cells (right)



Cl: Benign subcutaneous well-circumscribed tumor; location preferentially in the neck, upper back or shoulders.

Hi:

- Solid nests and bundles of various proportion of CD34-positive spindle cells
- Entrapping of lobules of mature adipose tissue or fat vacuoles
- Wiry collagen between the adipocytes
- Basophilic mucinous stroma
- Spindled tumor cells show distinct loss of RB1

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BENIGN NEOPLASMS**Pleomorphic Lipoma (see Pleomorphic Liposarcoma)**

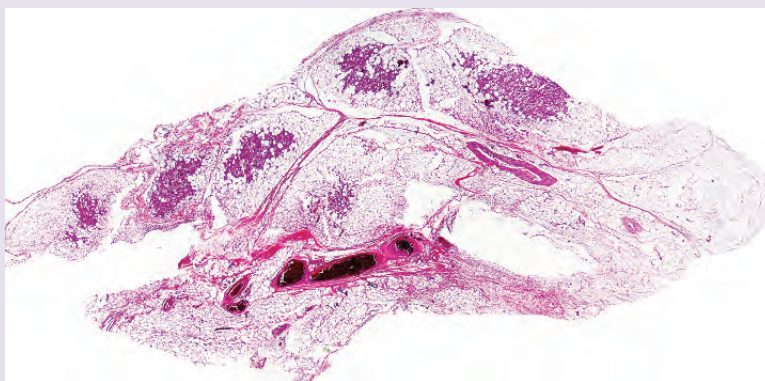
Pleomorphic lipoma may be interpreted as a morphological variant of spindle cell lipoma with hyperchromatic and floret-like tumor cells and loss of RB1. Mitotic activity is exceedingly low. There are no distinct pleomorphic lipoblasts as in pleomorphic liposarcoma.

Reference

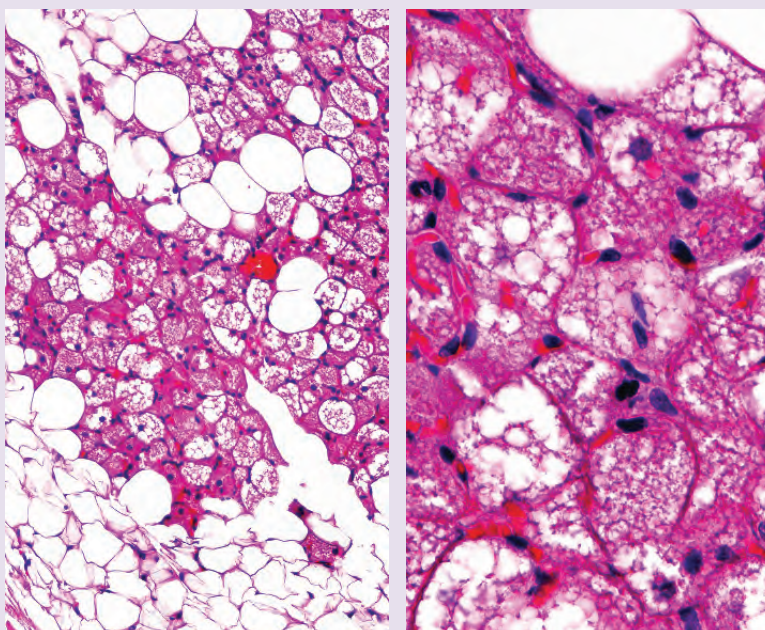
Griffin, T.D., Goldstein, J., and Johnson, W.C. (1992). Pleomorphic lipoma. Case report and discussion of "atypical" lipomatous tumors. *J Cutan Pathol* **19**(4): 330–3.

Hibernoma

Lobular
subcutaneous
tumor



Multivacuolated
tumor containing
normal adipocytes
(left) and
mulberry-like
granular
eosinophilic cells
(right)



Tumor of brown fat, which is especially abundant in newborns and decreases in adults. Its primary function is thermoregulation. Whereas white adipocytes contain a single lipid droplet,

brown adipocytes contain numerous smaller droplets. The higher number of mitochondria, which contain iron, results in the brown appearance.

MALIGNANT NEOPLASMS

Cl: Subcutaneous well-circumscribed tumors, preferentially on the trunk of young adults.

Hi:

- Macroscopically yellow-brown cutting surface
- Lobular tumor
- Large mulberry-like cells with abundant eosinophilic granular cytoplasm
- Variants: lipoma-like, spindle cell or myxoid type

DD: Granular cell tumor; liposarcoma; rhabdomyoma.

References

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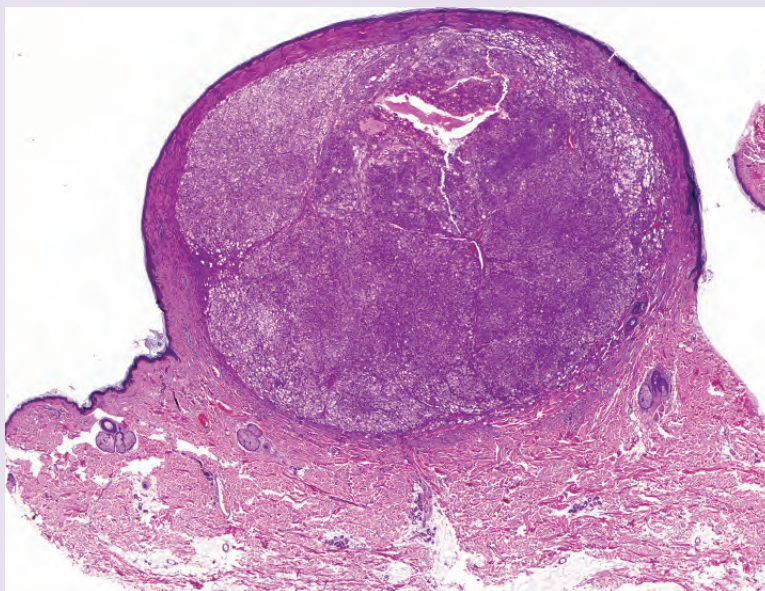
Malignant Neoplasms

Cutaneous Liposarcoma

In the skin, the most common liposarcoma is atypical lipomatous tumor (ALT). This is a well-differentiated liposarcoma and shows identical histopathological features to well-differentiated liposarcoma of the retroperitoneum, albeit with a completely different biological course: ALT of the skin does recur, but is benign. However, there are genuine liposarcomas of the subcutis, including pleomorphic and chondroid variants.

Cutaneous Liposarcoma

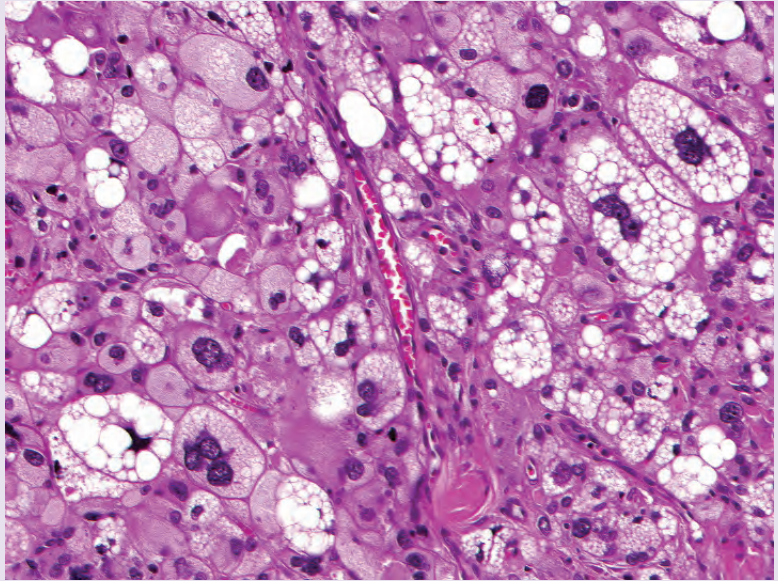
Nodular
exophytic
growing
dermal tumor



MALIGNANT NEOPLASMS

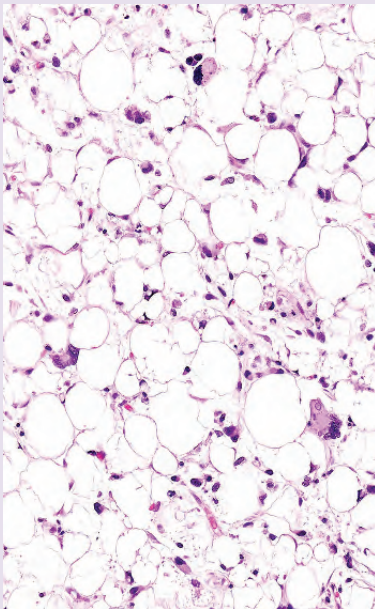
Cutaneous Liposarcoma

Multivacuolated
lipoblasts

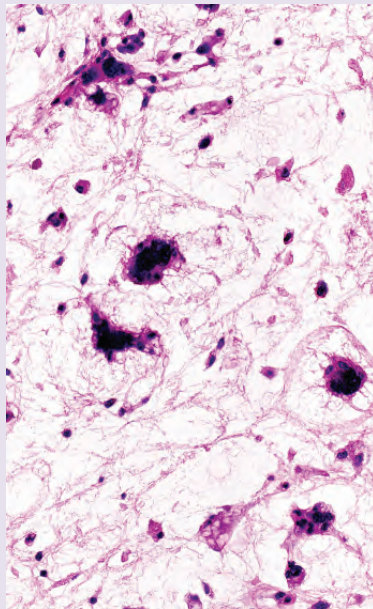


CI: Deep subcutaneous tumor, morphology mostly similar to large banal lipoma.

Variants of Liposarcoma



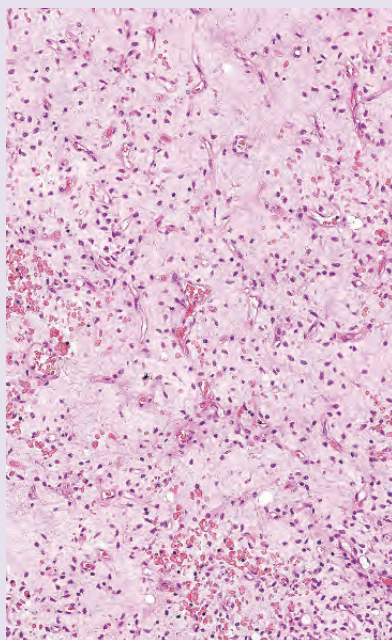
well differentiated



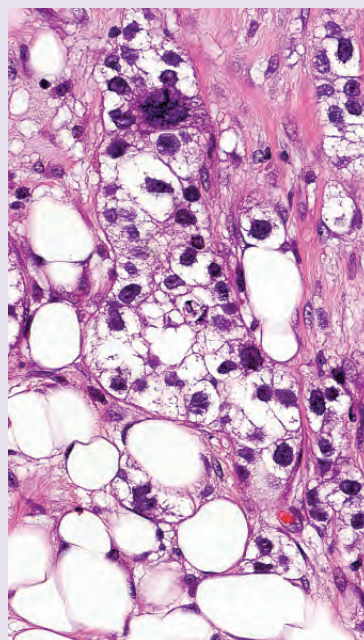
pleomorphic

MALIGNANT NEOPLASMS

Variants of Liposarcoma



myxoid



round cellular

Hi: Under low power, these tumors appear as mature adipose tissue or as “normal” lipomas, albeit with interspersed lipoblasts (“busy fat”). Lipoblasts are the hallmark cell type, containing cytoplasmic vacuoles with lipid, which cause wedge-shaped morphology of the nucleus. The nuclear polymorphism is variable, from low (ALT) to strikingly atypical (pleomorphic liposarcoma). High-grade liposarcomas show unequivocal signs of malignancy (mitotic activity, polymorphism, infiltrative growth). Various cytological subtypes can be differentiated.

- Well differentiated (ALT)
- Pleomorphic
- Myxoid
- Round cellular
- Chondroid
- Spindle cellular
- Mixed

Cytogenetic hallmarks of ALT and conventional liposarcoma are amplifications (FISH) of the *MDM2* and the *CDK4* genes that correlate with hyperexpression of their proteins. There is

co-expression of p16. Remarkably, pleomorphic liposarcoma does not show amplifications of *MDM2* and *CDK4*.

DD: Lipoma; other sarcomas; angiomyxoma.

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MALIGNANT NEOPLASMS

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CHAPTER 8

Muscle

CHAPTER MENU

Benign Neoplasms

Piloleiomyoma

Angioleiomyoma (see Vessels, Chapter 6)

Rhabdomyoma, Adult Type

Malignant Neoplasms

Rhabdomyosarcoma

Superficial Leiomyosarcoma

BENIGN NEOPLASMS**Benign Neoplasms**

Leiomyomas are benign tumors arising from structures containing smooth muscles (arrector

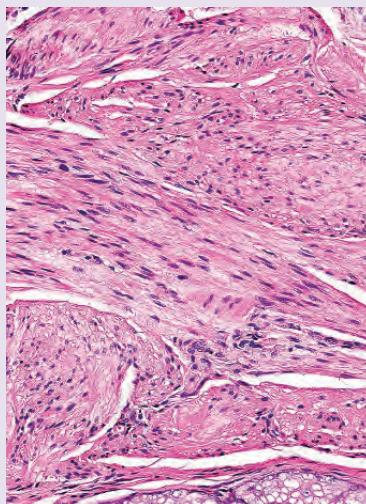
pili, tunica dartos of the scrotum, labia major, nipple, and blood vessels). The most common variant is pilar leiomyoma.

Piloleiomyoma (Pilar Leiomyoma)

Solitary (left) and multiple agminated leiomyomas (right)



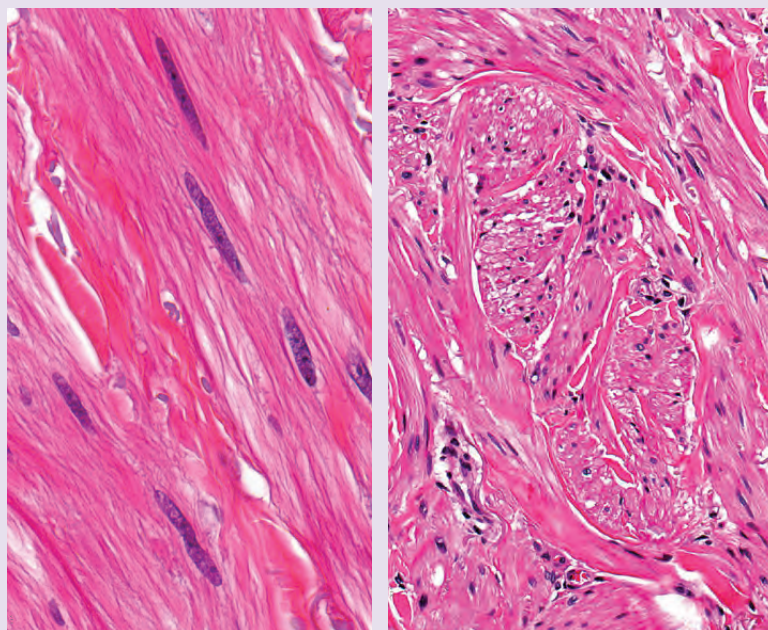
Fascicles of spindle-shaped smooth muscle cells. Longitudinal (left) and cross (right) section



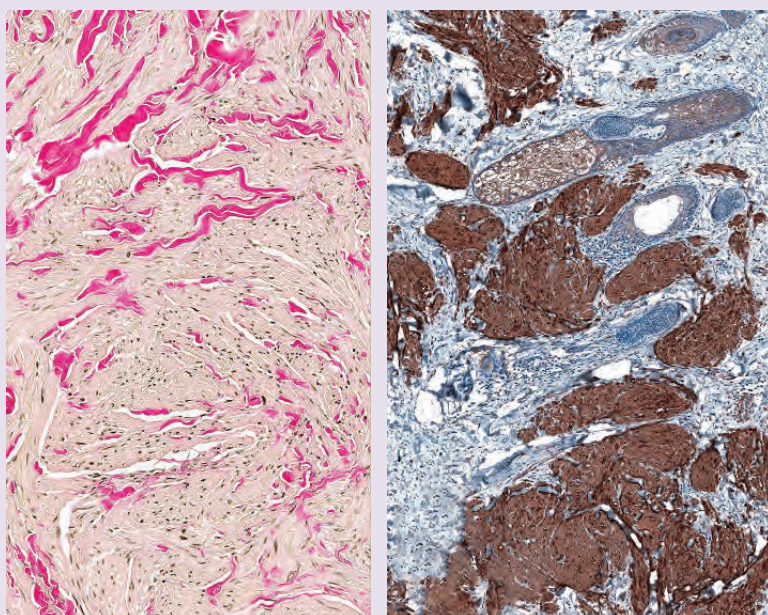
BENIGN NEOPLASMS

Piloleiomyoma

Fascicles of smooth muscle cells with typical cigar-shaped nuclei in longitudinal (left) and cross section (right)



van Gieson (left; yellow) and smooth muscle actin (ASMA) (right)



Fumarate hydratase deficiency (sporadic mutation or germline mutation) is a hallmark of a familial cancer syndrome. Atypical leiomyomas are considered to be borderline tumors or variants of low-grade cutaneous leiomyosarcoma, depending on grade and size of the tumor.

Cl: Solitary or multiple (zosteriform pattern), skin-colored or pink tender nodules.

Hi:

- Poorly circumscribed dermal tumor composed of fascicles of spindled smooth muscle cells
- Cells have blunt-ended cigar-shaped nuclei

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- Variants may show giant cells, myxoid changes, and atypical nuclei (atypical leiomyoma, ancient leiomyoma)
- Immunohistochemical positivity for desmin. α -SMA often positive
- Diffuse positivity for fumarate hydratase
- Sporadic and syndromic variants are fumarate hydratase negative, reflecting underlying mutation or germline mutation of FH gene, resulting in early onset of uterine leiomyomas and hereditary leiomyomatosis and renal cell cancer syndrome

DD: Angioleiomyoma; myofibroma; neural tumors.

References

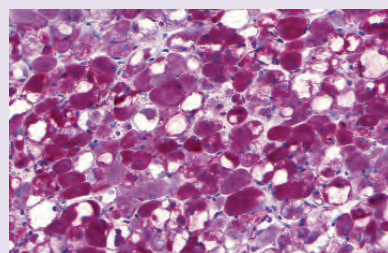
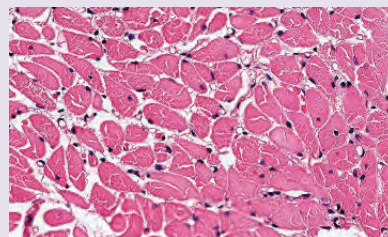
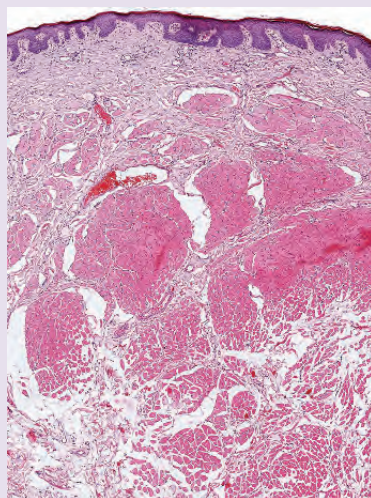
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Angioleiomyoma
(see Vessels, Chapter 6)

Rhabdomyoma, Adult Type

Nodules of
rhabdoid cells in
the dermis (left)

Rhabdoid cells
(right top),
ASMA positive
(right bottom)



Infantile and adult types have to be differentiated. Rhabdomyomas of adult skin are rare benign tumors of striated skeletal muscle. More common are rhabdomyomatous hamartomas of extracutaneous organs (heart) in association with tuberous sclerosis in children.

CI: In adults, mostly solitary dermal and subcutaneous lesions preferentially affect the head and neck area.

Hi: The histological picture shows foci of skeletal muscle tissue in the dermis. There are age-dependent variations: in the adult type, fascicles

MALIGNANT NEOPLASMS

of mature striated myofibers and polygonal, densely packed cells with abundant granular eosinophilic cytoplasm and eccentric nuclei are seen. The fetal type shows immature spindle-shaped skeletal muscle cells in a myxoid background. Mitotic activities or cellular atypias are lacking in all types.

DD: Rhabdomyosarcoma; granular cell tumor.

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Mengoli, M.C., Jukna, A., and Cesinaro, A.M. (2016) Rhabdomyoma of the lip: a case report with review of the literature. *Am J Dermatopathol* **38**(2): 154–7.

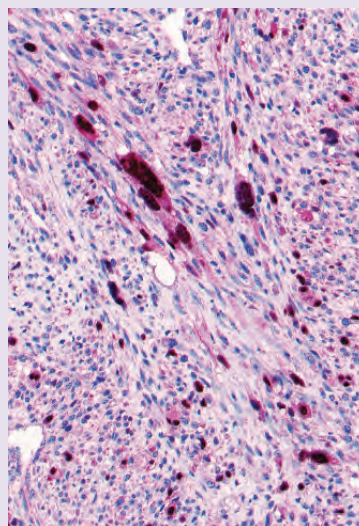
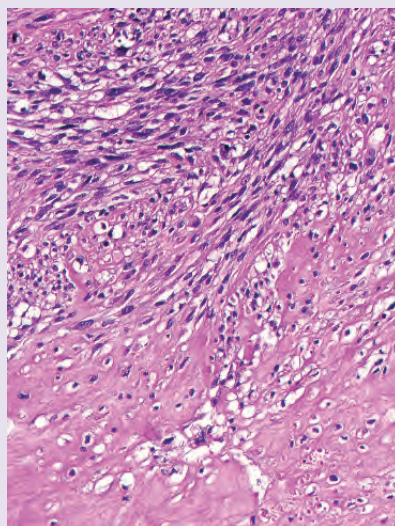
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Malignant Neoplasms

Rhabdomyosarcoma

Proliferation of atypical skeletal muscle tissue (left), myf4-positive (right)



This malignant neoplasm of childhood rarely arises primarily in the skin. Histologically, various subtypes have been reported, including spindle or epithelioid cell variants. Immunohistochemistry shows reactivity for muscle actin, desmin, and myf4.

References

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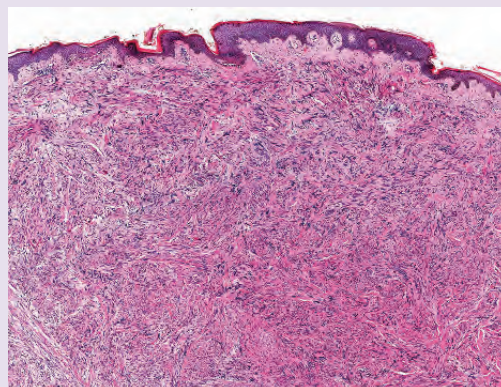
MALIGNANT NEOPLASMS

Superficial Leiomyosarcoma

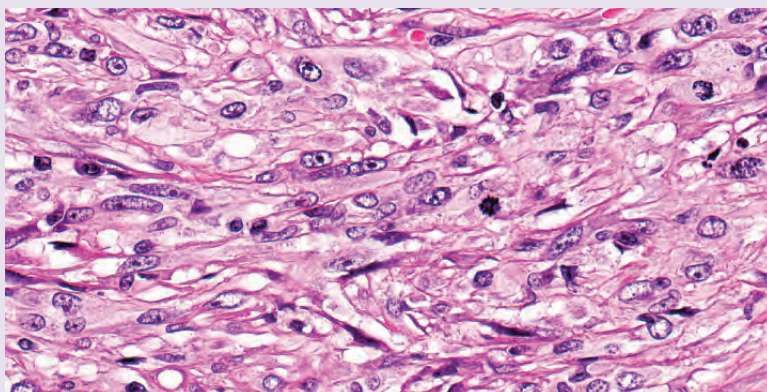
Tumorous mass on the hand (left)



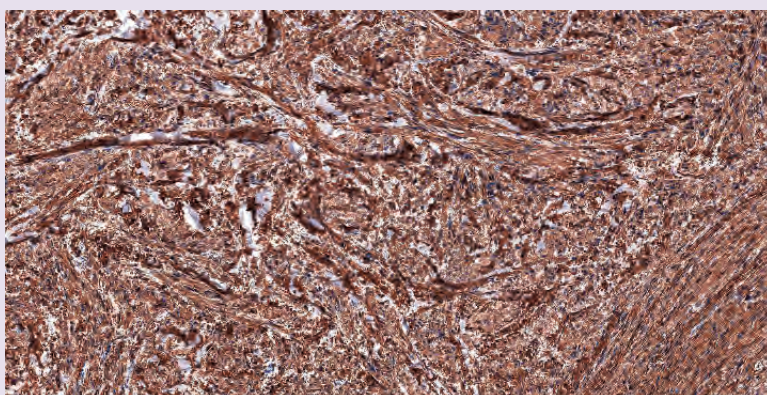
Poorly circumscribed dermal tumor mass (right)



Densely packed pleomorphic spindle cells



Smooth muscle actin (ASMA)



CI: Dermal or subcutaneous pink nodules or tumors preferentially on the extremities of adults, arising from hair or blood vessel muscles. Recent findings suggest that superficial dermal leiomyosarcoma is a low-grade sarcoma

showing morphological overlap with atypical leiomyoma. Nosologically, there is a clear-cut difference between low-grade superficial dermal leiomyosarcoma and leiomyosarcoma of soft tissue.

MALIGNANT NEOPLASMS

Hi:

- Poorly circumscribed tumor; tumor silhouette resembling leiomyoma
- Invasive growth pattern
- Fascicles of densely packed spindle cells, with abundant eosinophilic clear cytoplasm
- Pleomorphic, blunt-ended nuclei, sometimes vesicular with prominent nucleoli
- High mitotic activity
- Tumor cells positive for alpha-SMA and desmin. Focal cytokeratin positivity in larger anaplastic tumors
- Cutaneous metastasis of soft tissue leiomyosarcoma may present with identical morphology

Immunohistochemistry: Tumor cells positive for alpha-SMA and desmin. Focal cytokeratin positivity in larger anaplastic tumors.

DD: Dermatofibrosarcoma protuberans; leiomyoma; fibrous histiocytoma; malignant melanoma; granular cell tumor.

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CHAPTER 9

Nerves

CHAPTER MENU

Benign Neoplasms	Pacian Neurofibroma (Pacina)
Schwannoma (Neurilemmoma)	Malignant Neoplasms
Solitary Neuroma ("Palisaded Encapsulated Neuroma")	Malignant Peripheral Nerve Sheath Tumor
Variant: Traumatic Neuroma	(Malignant Schwannoma)
Granular Cell Tumor (Abrikossoff)	Malignant Granular Cell Tumor
Dermal Nerve Sheath Myxoma	Neuroendocrine Neoplasm
(Myxoid Neurothekeoma)	Primary Neuroendocrine (Merkel Cell, Trabecular)
Variant: Cellular Neurothekeoma	Carcinoma of the Skin

Benign Neoplasms

Neurofibroma and schwannoma are the most common neoplasms of the nerve sheath. They are composed of several components, mostly

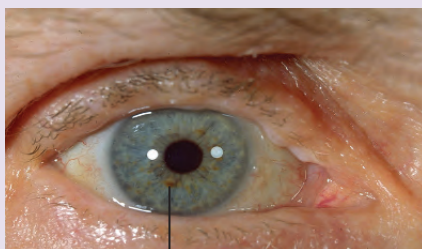
Schwann cells and endoneurial and perineurial fibroblasts. Axons may be present, albeit in rather low quantities.

Neurofibroma and Recklinghausen's Disease (Phakomatosis)

Kypho-
scoliosis (left).
Large
neurofibroma of
the planta (right)

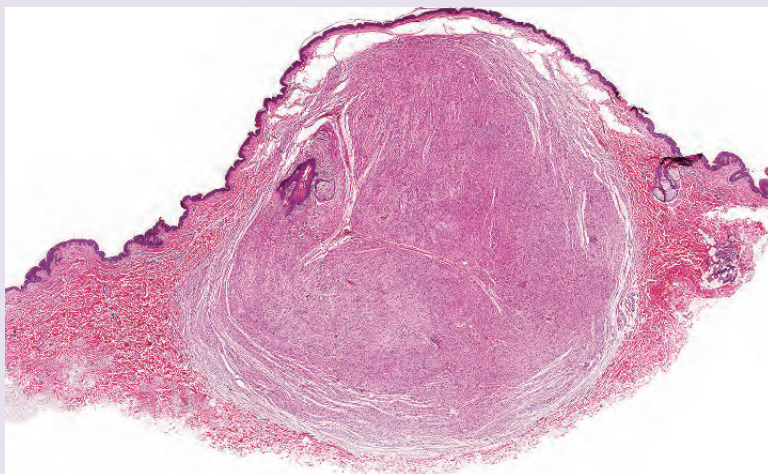


Multiple
neurofibromas in
Recklinghausen's
disease



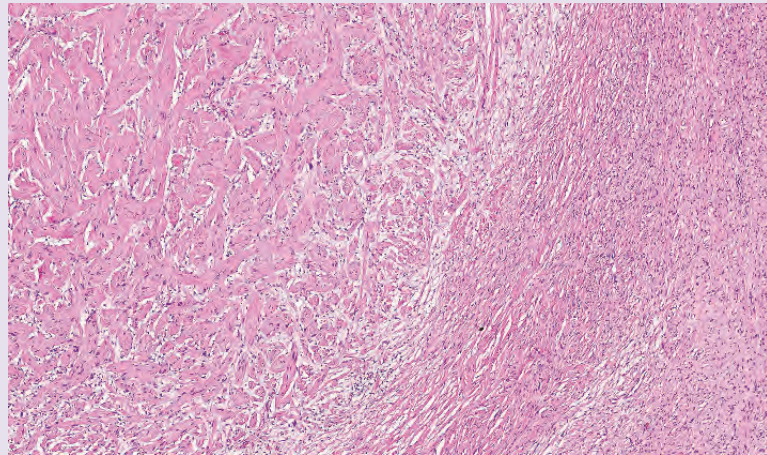
Brown Lisch nodules (iris hamartomas)

Dermal tumor,
sparing the
papillary dermis
and showing
capsule-like
condensation of
perineurial tissue
at the outer
margin



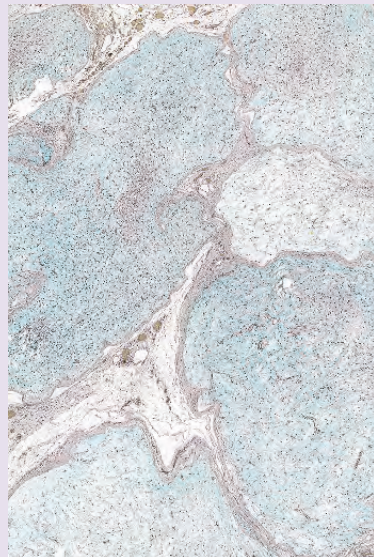
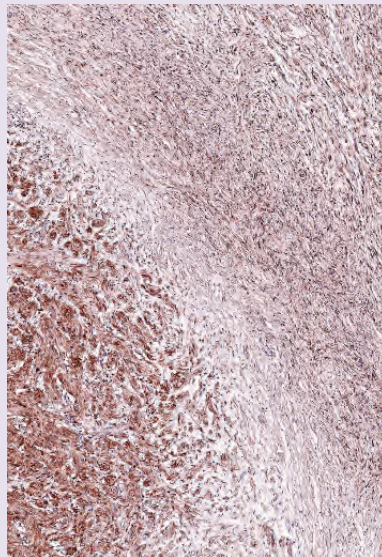
Neurofibroma and Recklinghausen's Disease (Phakomatosis)

Distinct wavy nuclei of Schwann cells and interspersed fibroblasts in obliquely (left) and longitudinally (right) cut fascicles



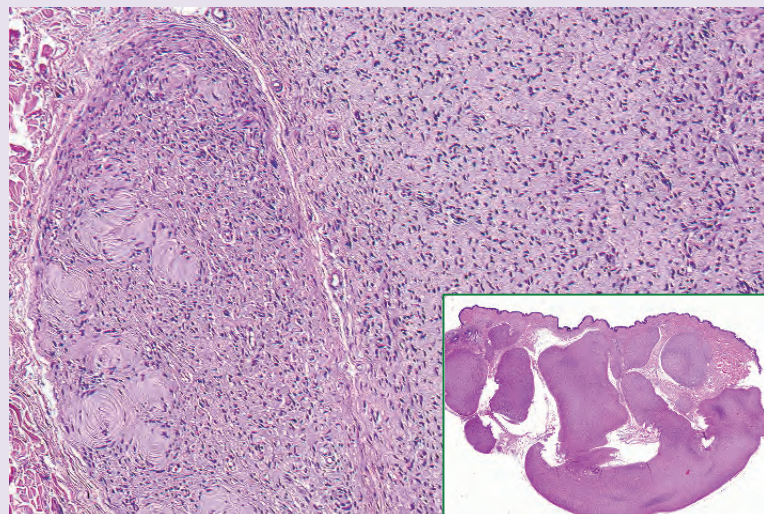
S100 + Schwann cells in neurofibroma (left)

Alcian blue staining of myxoid stroma (right)



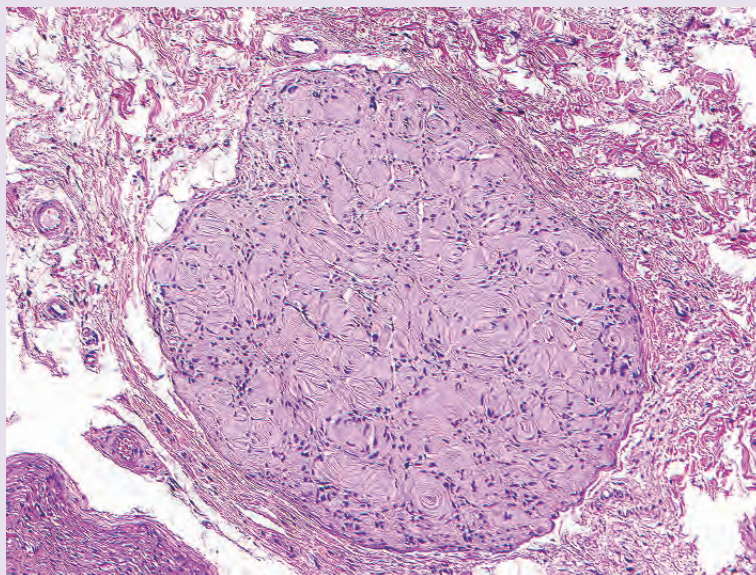
Plexiform Neurofibroma

Large dermal tumor mass (inset), composed of fascicles and bundles of spindle-shaped nerve cells



Plexiform Neurofibroma

Whorly plexiform growth pattern of spindle cells and fibrous stroma reaction



Neurofibromas are proliferations of Schwann cells, endoneurial and perineurial cells, few axons, and mast cells. Sporadic forms have to be differentiated from neurofibromas associated with Recklinghausen's phacomatosis (NF 1 and NF 2), which is an inherited autosomal dominant disorder. NF 1 presents with skin, neurological, and orthopedic symptoms. The diagnosis can be made if two or more of the following diagnostic criteria are present.

- Six or more café-au-lait spots
- 1–2 neurofibromas or 1 plexiform neurofibroma
- Axillary or inguinal freckles
- Optic nerve glioma
- Lisch nodules (iris hamartomas)
- Bone deformity and kyphoscoliosis

Cl: Multiple, molluscoid, polypoid, sometimes pedunculated, soft, pink or skin-colored tumors, preferentially on the trunk. Some tumors can be pushed into the skin (herniation from the subcutis). Large plexiform neurofibromas may affect large body areas or involve an entire extremity.

Hi:

- Circumscribed dermal tumor, surrounded by perineurial outer fibrous sheath simulating encapsulation
- Fusiform spindle cells (Schwann cells) with distinct cytoplasmic membrane and wavy nuclei with tapered ends

- Eosinophilic pale, myxoid or fibrotic stroma
- No Verocay bodies
- No mitoses
- Stroma rich in mast cells
- Fine, scattered nerve fibers may be present
- Variants of neurofibroma include plexiform, diffuse, myxoid, sclerotic, granular cellular, epithelioid and "ancient" forms with bizarre giant cells

Immunohistochemistry: Diffuse positivity for S100 (Schwann cells) and CD34 (stroma and perineurial fibroblasts). Few neurofilament positive axons.

DD: Large skin tag (acrochordon); dermatofibroma; schwannoma; smooth muscle neoplasms; melanocytic nevus; hypertrophic scar.

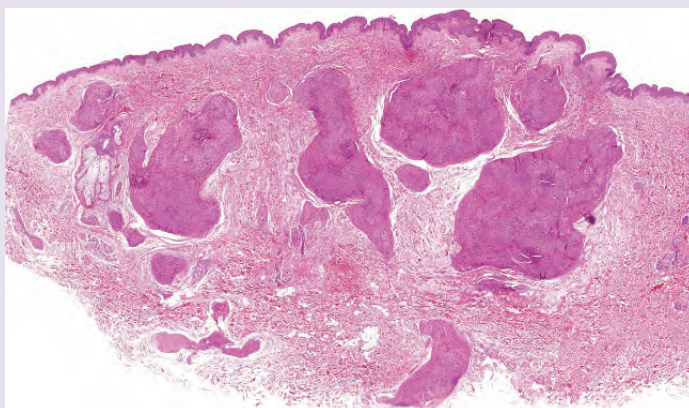
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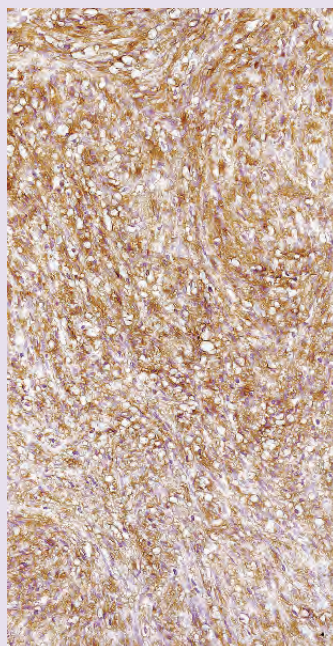
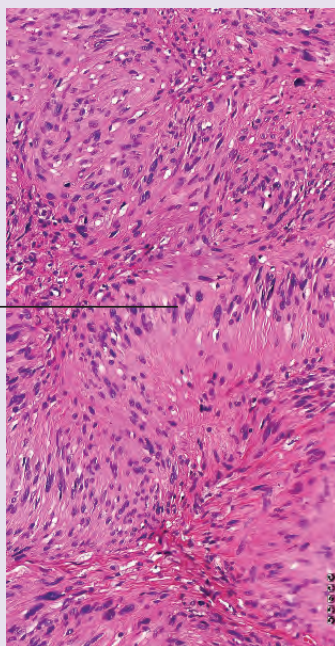
Schwannoma (Neurilemmoma)

Well
circumscribed
nodular
proliferations
of Schwann
cells



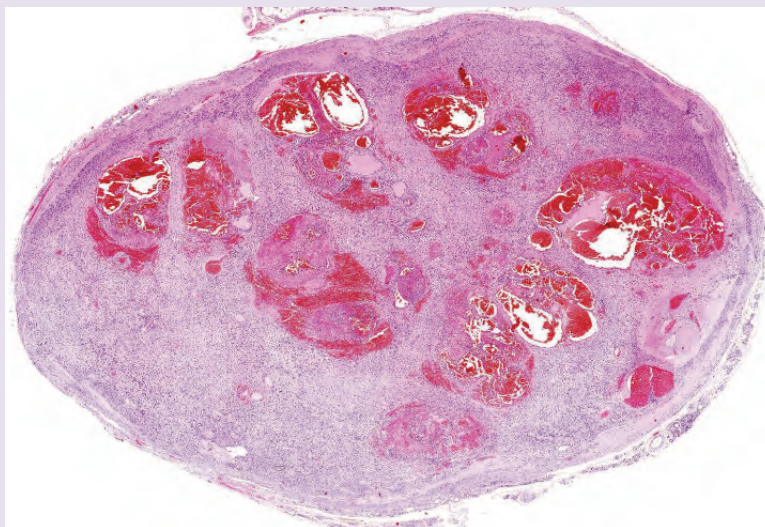
Palisading nuclei
(Verocay bodies)

S100 (right)

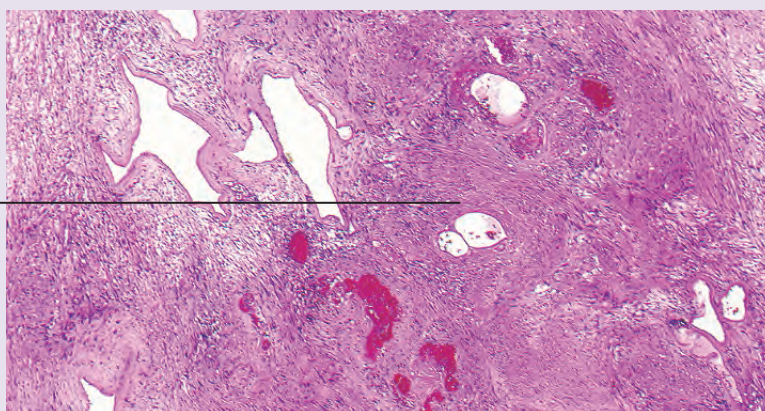


"Ancient" Schwannoma

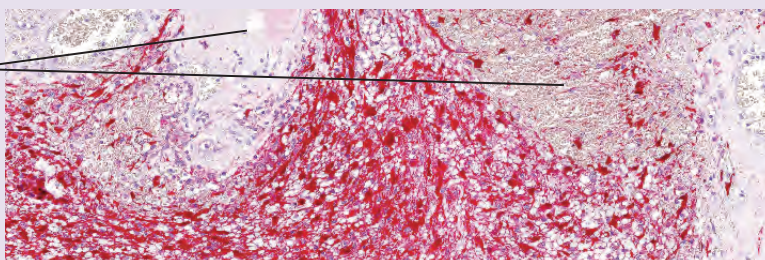
Degenerative changes



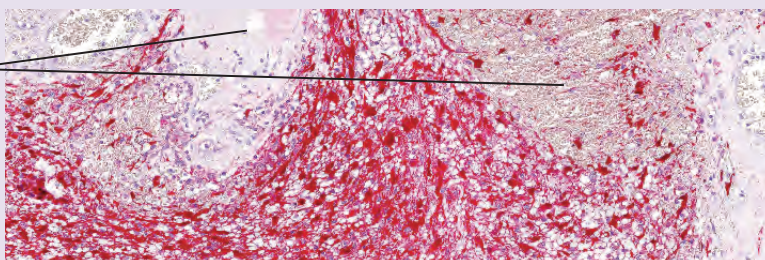
Ectatic vessels and thrombi. Antoni type B neuroid tissue



Edematous stroma and necrosis



S100+ Schwann cells



Schwannomas represent neural Schwann cell proliferations with embedded axons and perineurial fibroblasts. They are genuine nerve sheath tumors showing morphological overlap with genuine neuromas.

CI: Mostly well-demarcated solitary tumors in adults, located in the deep dermis or subcutaneous tissue of the head and neck area or the extremities. Close attachment to peripheral nerves may be responsible for tenderness.

Hi:

- Well-demarcated nodular proliferation of S100-positive Schwann cells in the dermis or subcutaneous tissue
- CD34-positive perineurial outer sheath
- Adjacent nerves may be present
- Schwann cells show elongated nuclei with roundish poles and fine chromatin
- Tumor with a dual morphological pattern:
 - *Antoni A areas*: loosely textured fascicles with palisading nuclei aligned in parallel arrays and bordered on both sides by amphophilic masses (Verocay bodies)
 - *Antoni B areas*: fewer cellular areas, myxoid, edematous, without conspicuous aligning of nuclei
- Besides common schwannoma, there are several histological subtypes, including cellular, myxoid, plexiform psammomatous (associated with Carney's complex) and "ancient" schwannoma. The latter is composed of Antoni type B tissue and shows cellular atypia, degenerative changes, ectatic vessels with thrombi, stromal edema, and inflammatory infiltrate with many macrophages
- Vessels with thickened vessel walls and fibrosis may be present
- Neurofilament-positive axons in low numbers

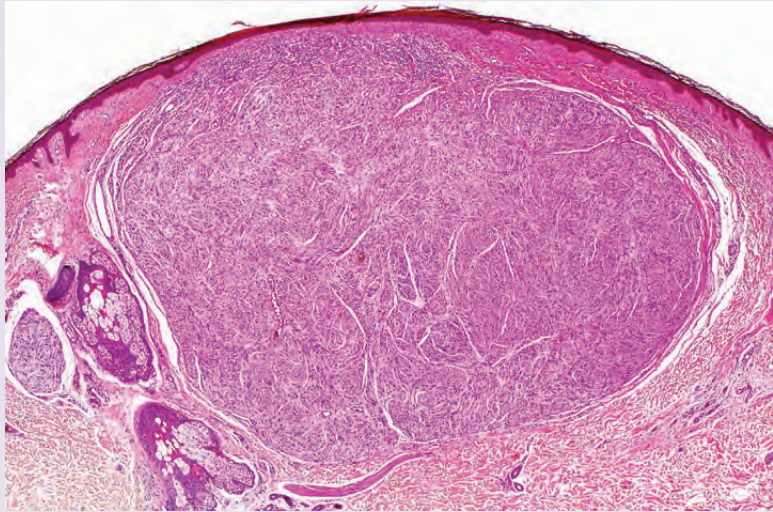
DD: Encapsulated, palisaded neuroma; amputation neuroma; neurofibroma; dermatofibroma; angioleiomyoma.

References

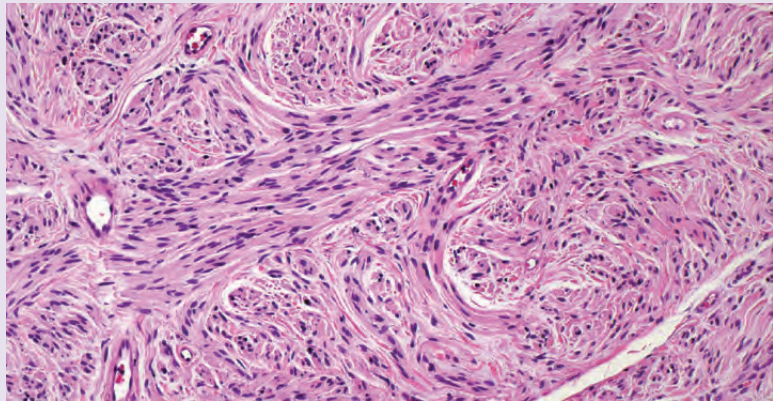
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Solitary Neuroma ("Palisaded Encapsulated Neuroma")

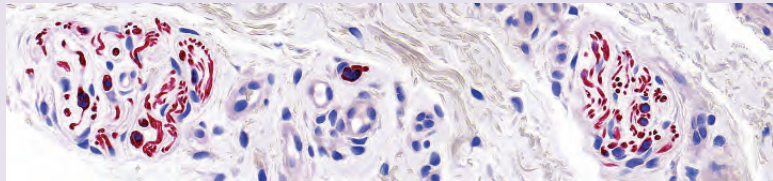
Non-capsulated
dermal nodule
with distinct
clefts



Interweaving
Schwann cell
fascicles
showing axons
and clefts



Neurofilament-
positive axons



Cl: Small protuberant nodules with the clinical aspect of a papillomatous nevus. Predilection sites are the head and neck area. The tumor is a genuine dermal neuroma.

Hi:

- Sharp circumscription, but no encapsulation
- Densely packed interweaving nerve fascicles
- Prominent shrinkage clefts between nerve fascicles
- Neurofilament-positive axons throughout the tumor

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Variant: Traumatic Neuroma

Cl: Traumatic neuromas are painful skin-colored, broad-based firm nodules following injury. They represent an incomplete repair process following nerve destruction and are related to rudimentary supernumerary digit, which develops at the lateral aspect of the hand.

Hi:

- Poorly circumscribed dermal tumor
- Confluent nerve fascicles with neurofilament-positive axons
- Fibrous stroma next to adjacent scar
- No Verocay bodies

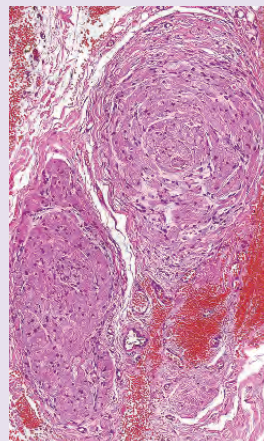
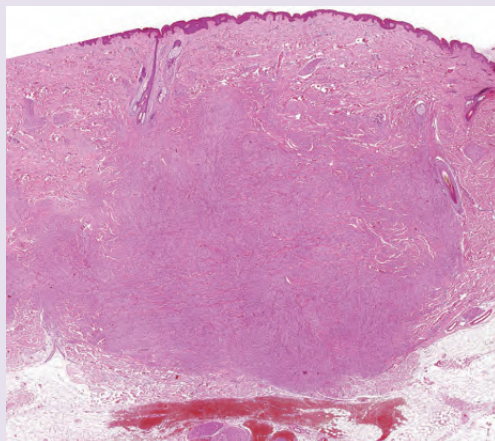
DD: Supernumerary digit; schwannoma; neurofibroma; angioleiomyoma.

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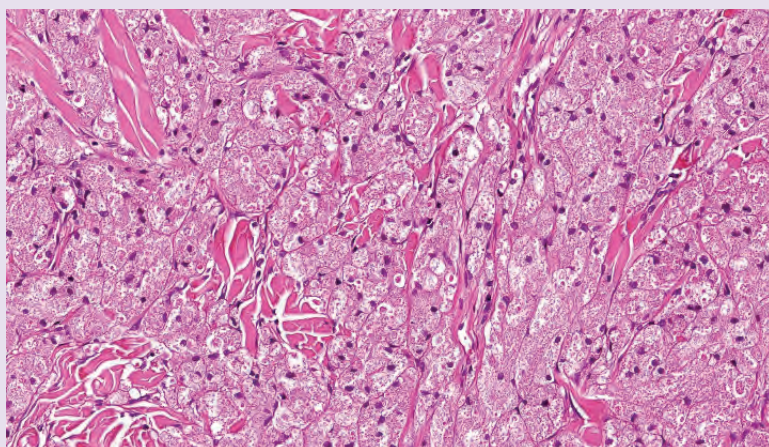
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Granular Cell Tumor (Abrikossoff)

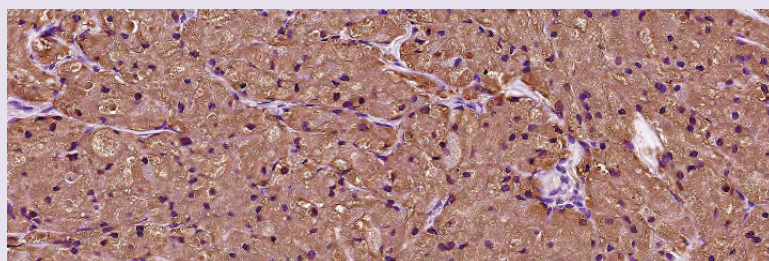
Moderate
epidermal
hyperplasia
overlying dermal
tumor (left) with
fascicular
differentiation
(right)



Densely packed
polygonal cells
with granular
cytoplasm (top
right and mid)



S100-positive
tumor cells



This is a genuine nerve sheath tumor which was originally considered to be derived from striated muscle cells (“granular cell myoblastoma”). Tumor cells show schwannian features with an abundance of lysosomes within the cytoplasm.

CI: The tongue is the most common localisation for mostly solitary and sometimes multiple tumors, which also can appear on the skin and in extracutaneous organs. Malignant variants are rare.

Hi:

- Pseudocarcinomatous hyperplasia, sometimes with verrucous features
- Compact dermal tumor, extending into the subcutis
- Large, densely packed polygonal tumor cells with eosinophilic granular cytoplasm
- Uniformed small, round, centrally located nuclei
- No mitotic activity
- Cytoplasmic granules stain positive for PAS
- Schwannian tumor cells are positive for S100 protein; cross-reaction with CD68 may be misleading

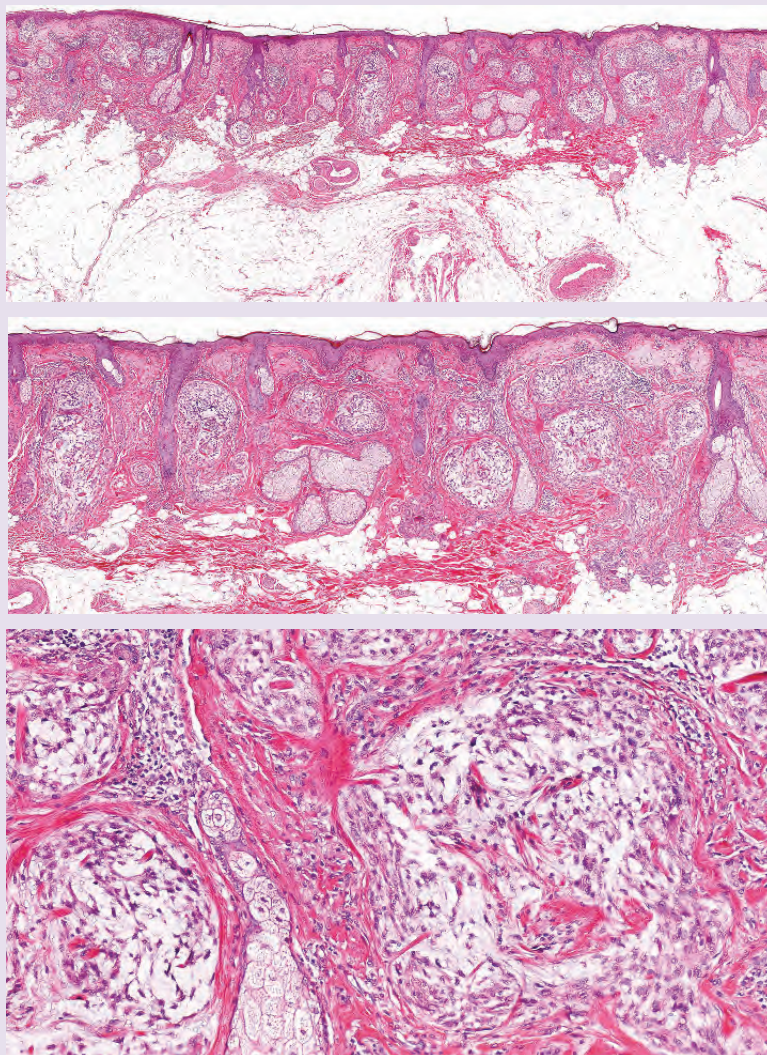
DD: Malignant granular cell tumor; xanthoma; squamous cell carcinoma; basal cell carcinoma; leiomyoma; renal cell carcinoma; granular cell variants of other tumors.

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Dermal Nerve Sheath Myxoma (Myxoid Neurothekeoma)

Nests of spindle cells in myxoid stroma (top, mid) separated by collagen septa (bottom)



The term *neurothekeoma* comprises a spectrum of histogenetically different benign neoplasms, ranging from hypocellular myxoid (“classic” neurothekeoma) to hypercellular lesions with immature cells in a collagenous stroma (cellular neurothekeoma). Recent findings suggest that myoid neurothekeoma and cellular neurothekeoma show no histogenetic relationship.

The latter most likely is a variant of histiocytoma/dermatofibroma (with conspicuous immuno-histochemical co-expression of NKIC3 and alpha-SMA).

CI: Small, asymptomatic dome-shaped, firm, pink or red-brown papules and nodules, mostly on the head, neck or upper extremities of young women.

Hi:

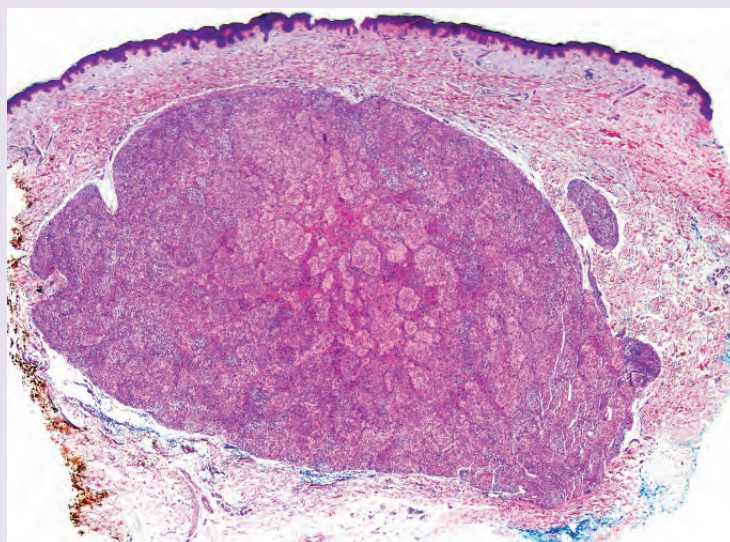
- Multilobulated myxoid tumor in the dermis
- S100-positive stellate and spindled cells with hyperchromatic nuclei within a myxoid stroma
- Collagenous septa separating myxoid nests

References

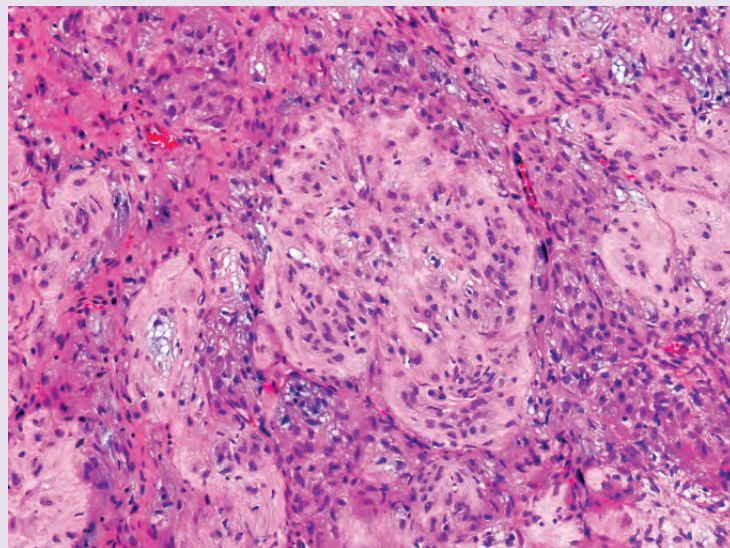
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Variant: Cellular Neurothekeoma

Nodular dermal tumor



Nests of histiocytoid cells with slight epithelioid morphology in an eosinophilic stroma



Cellular neurothekeoma, which histologically imitates dermal Spitz nevus, is an important differential diagnosis.

Hi:

- Cellular nests of histiocytoid cells, imitating dermal Spitz nevus
- Collagenous septa
- Low mitotic activity

Immunohistochemical positivity for NKIC3, alpha-SMA, and CD68.

References

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Pacinian Neurofibroma (Pacinoma)

Cl: The clinical setting is identical with genuine neurofibroma.

Hi: Hallmarks are tumor foci that exhibit Pacinian differentiation, imitating the morphological pattern of Pacinian bodies.

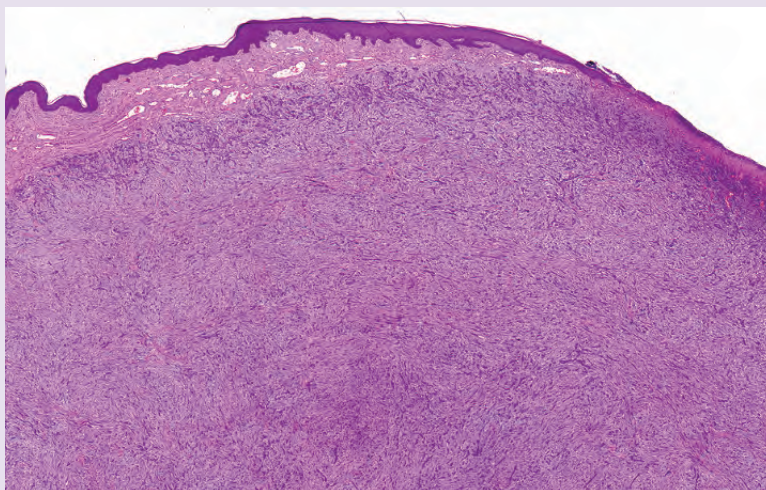
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Malignant Neoplasms

Malignant Peripheral Nerve Sheath Tumor (Malignant Schwannoma)

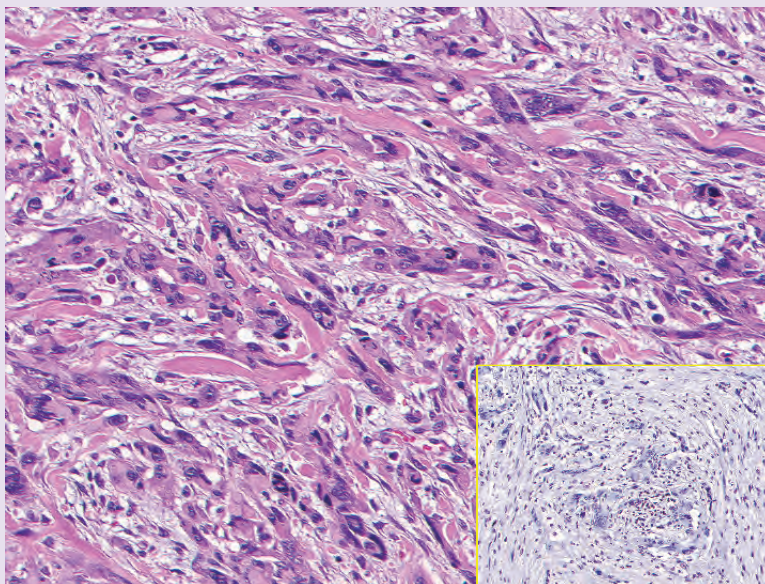
Circumscribed dermal tumor



Malignant Peripheral Nerve Sheath Tumor (Malignant Schwannoma)

Undifferentiated spindle shaped tumor cells in a sparse myxoid stroma

Inset:
characteristically unmethylated tumor cells (negative for H3K27me3; polyclonal antibody)



CI: Large tumor masses involving the dermis and the adjacent upper subcutis.

Hi:

- Spindle-shaped atypical pleomorphic cells
- S100 positive
- Scarce myxoid stroma
- Tumor cells characteristically lack tri-methylation of lysine-residue in histone 3 complex (negative for H3K27me3; polyclonal antibody)

DD: Melanoma; fibrosarcoma.

References

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Malignant Granular Cell Tumor

Cl: In most cases, this tumor variant is diagnosed retrospectively, after multiple metastases have occurred.

Hi: Remarkably, it is exceedingly difficult to differentiate atypical granular cell tumor unequivocally from its malignant counterpart without the help of ancillary clinical information. Both tumors may show significant morphological overlap. Mitotic activity and pleomorphism may be low in the malignant variant, although mitoses and atypical nuclei as well as tumor size should be taken as signs of caution.

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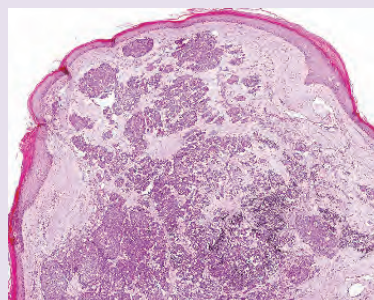
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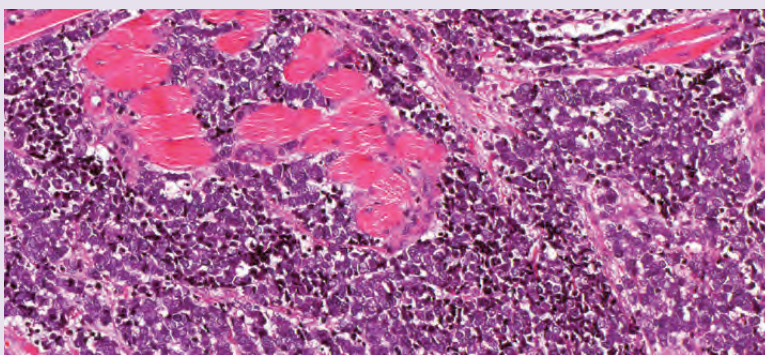
Neuroendocrine Neoplasm

Primary Neuroendocrine (Merkel Cell, Trabecular) Carcinoma of the Skin

Tumor plaques on cheek and nose



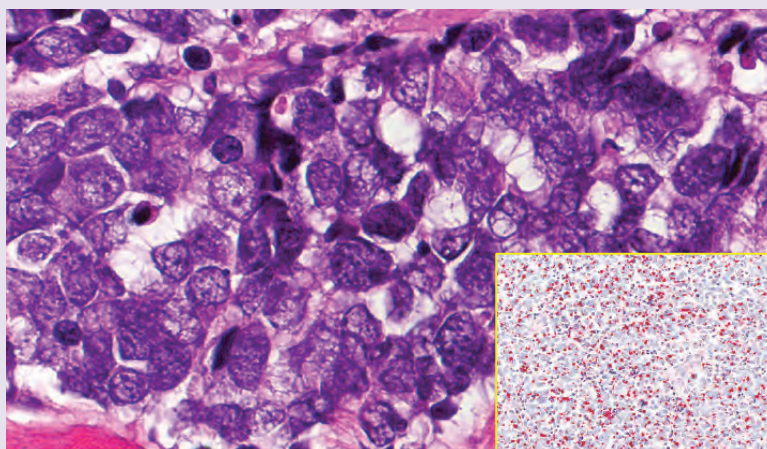
Sheets and clusters of infiltrating cells in the dermis (top right and bottom)



Primary Neuroendocrine (Merkel Cell, Trabecular) Carcinoma of the Skin (Cutaneous APUDoma)

Uniform basophilic cells with granular vesicular nuclei and scant cytoplasm

Inset: CK20 positive tumor cells (paranuclear staining)



APUD (Amine Precursor Uptake and Decarboxylation) cells are endocrine active cells in the epithelia of tissue apart from endocrine organs. Merkel cells are intraepithelial neuroendocrine cells. Most cases of Merkel cell carcinoma have shown integration of Merkel cell polyoma virus (MCPyV) DNA into the tumor genome, suggesting a pathogenetic role. The tumor cells express both features of neuroendocrine and epithelial differentiation. Merkel cell carcinoma has been reported in association with poroma, Bowen, squamous cell carcinoma, basal cell carcinoma, seborrheic and actinic keratosis and other epithelial or adnexal tumors and intraepidermal forms.

Cl: The head and neck of elderly patients are most commonly affected by this rare plaque-like or dome-shaped, rapidly growing, infiltrating and ulcerating tumor, which shows early metastases in regional lymph nodes and visceral organs. Prognosis is bad if not excised early and totally.

Hi:

- Sheets and clusters of infiltrates in occasionally trabecular pattern, in the dermis, extending into the subcutis
- Monomorphous uniform, round basophilic small to medium-sized cells with granular vesicular nuclei and scant cytoplasm
- Numerous mitoses and apoptotic cells
- Occasional focal squamous differentiation
- The Azzopardi phenomenon (basophilic granular nuclear DNA lacing the wall of small vessels), found in small cell carcinoma of the lung, is

typically lacking in most cases of cutaneous Merkel cell carcinoma

Immunocytochemistry: Neurofilament, chromogranin, synaptophysin, Cytokeratin 20 (paranuclear dot or membranous staining pattern), BerEP4, neuron-specific enolase. Insulinoma M1 (InsM1) is a new important marker for neuroendocrine differentiation.

Electron microscopy: Neurosecretory granules.

DD: Cutaneous (B-cell) lymphoma, other neuroendocrine carcinomas (lung); sweat gland carcinoma; melanoma.

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CHAPTER 10

Mast Cells

CHAPTER MENU

Solitary Cutaneous Mast Cell Proliferation

Cutaneous Mastocytoma

Diffuse Cutaneous Mast Cell Proliferations

Urticaria Pigmentosa (Juvenile Maculopapular
Mastocytosis)

Telangiectasia Macularis Eruptiva Perstans (Adults)

Systemic Mast Cell Proliferation

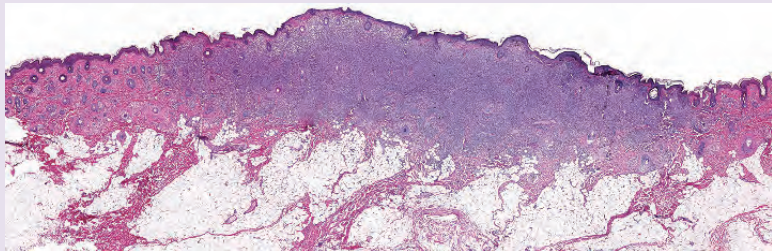
Involvement of Skin and Bone Marrow

Solitary Cutaneous Mast Cell Proliferation

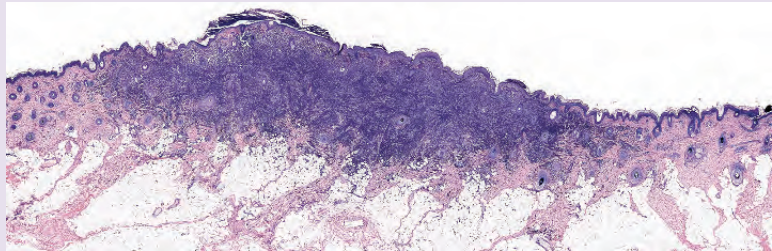
Cutaneous Mastocytoma

Red plaque on
the calf of a
child (left)

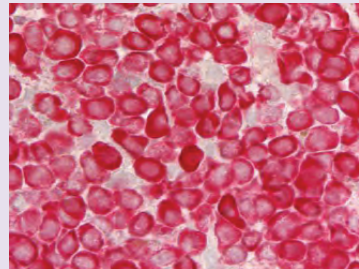
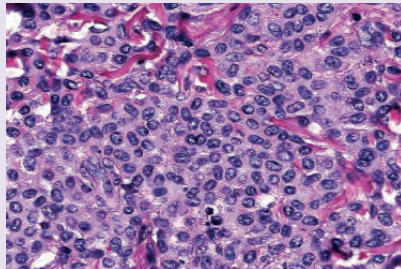
Sign of Darier
following rubbing
(right)



Densely packed
mast cells.
Hematoxylin-
eosin (top)
and Giemsa
(below)



Monomorphic
infiltrate of mast
cells (left),
stained for
naphthol-ASD-
chloroacetate-
esterase
(Leder stain)
(right)



Cl: Red-brown plaques or nodules, which markedly swell or even form blisters upon rubbing or other types of mechanical irritation (Darier's sign).

Hi:

- Cellular diffuse dermal infiltrate
- Monotonous proliferation of round or cuboidal mast cells with granular cytoplasm
- Giemsa, toluidine blue, naphthol-ASD-chloroacetate esterase (Leder) or mast cell tryptase stain allow identification of mast cells
- Immunohistochemical staining for CD117 (c-kit) is the most reliable mast cell stain

DD: Melanocytic nevus; cutaneous (B-cell) lymphoma; Langerhans cell histiocytosis.

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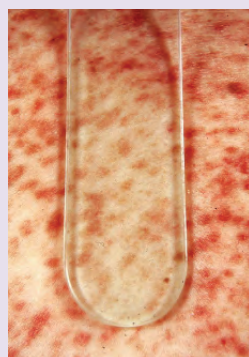
Ueng, S.H. and Kuo, T.T. (2004) An unusual mastocytoma with massive eosinophilic infiltration: identification with immunohistochemistry. *Am J Dermatopathol* **26**(6): 475–7.

Diffuse Cutaneous Mast Cell Proliferations

Urticaria Pigmentosa (Juvenile Maculopapular Mastocytosis)

Urticaria pigmentosa in a child (left). Lesions turning light brown under diaphanoscapy (mid).

Adult telangiectasia macularis eruptiva perstans (right)



Telangiectasia Macularis Eruptiva Perstans (Adults)



The juvenile form tends to regress spontaneously, whereas in adults the disease persists and frequently involves extracutaneous sites (liver, bone, blood – mast cell leukemia) and may show systemic symptoms such as pruritus, flushing, diarrhea, tachycardia or circulatory collapse due to the release of mediators from activated mast cells (histamin, serotonin, hydroxytryptamine). Check for serum tryptase.

Cl: Hundreds of small red-brown papules, showing light brown color when made anemic under diaphanoscapy. When mediators are released from mast cells by mechanical rubbing or scratching or by medical (non-steroidal antiphlogistics) or alimentary stimuli (banana, alcohol), the lesions become slightly elevated (Darier's sign) or may show blister formation. Palms, soles, and face usually are spared.

Hi: In some cases, the increased number of mast cells between collagen bundles of the dermis is not conspicuous and cannot be detected without special stains: Giemsa, toluidine blue or naphthol-ASD-chloroacetate esterase (Leder) stain, CD117 (c-kit).

- Upper and mid dermis
- Sleeve-like accumulation of monomorphous mast cells preferentially around vessels
- Dilated vessels
- Scattered eosinophils may be present, which should not be confused with bone marrow-derived mast cell precursors with eosinophilic cytoplasm, lacking the lobated nucleus typical for eosinophils
- Pigment in the basal layer

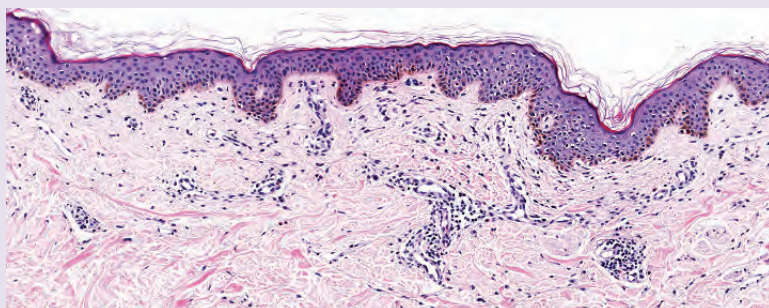
DD: Multiple leiomyomas; multiple adnexal tumors; Langerhans cell histiocytosis; myelomonocytic leukemia.

References

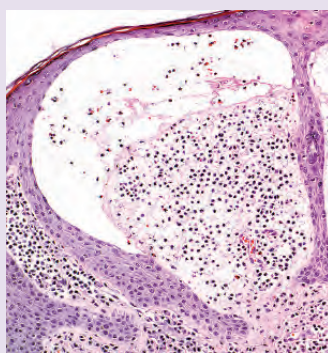
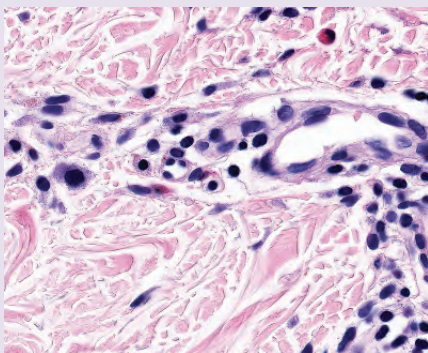
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Urticaria Pigmentosa and Telangiectasia Macularis Eruptiva Perstans (TMEP) (Adults)

Sleeve-like perivascular infiltrates of mast cells with overlying hyperpigmented epidermis

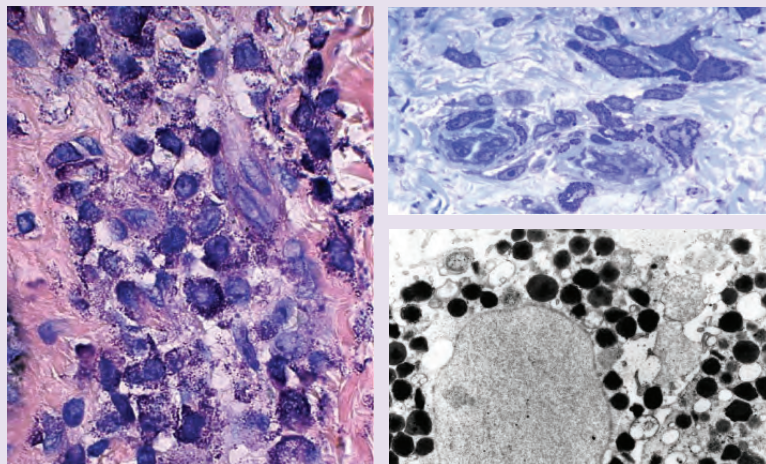


Perivascular accumulation of mast cells (left). Blistering following rubbing (right)



Urticaria Pigmentosa

Mast cells with typical granules. Giemsa (left). Semithin section (right top) and electron microscopy (right bottom)



TMEP is nosologically closely related to urticaria pigmentosa, with similar clinical and histopathological presentation. The clinical setting is much more obvious to the eye than the subtle histopathological changes (“invisible dermatosis”) for the pathologist.

Cl: Mostly in adults, multiple distinct or confluent small red-brown macules, patches or papules with telangiectases.

Hi:

- Hyperpigmentation of the basal layer
- No increase of melanocytes

- Subepidermal scant splaying of mast cells
- Accompanying telangiectasias
- Eosinophils
- Mast cells positive for CD117 (c-kit)

DD: See urticaria pigmentosa.

Systemic Mast Cell Proliferation

Involvement of Skin and Bone Marrow

Red papules disseminated on the trunk (left). Proliferation of mast cells in the bone marrow (right)



For more detailed clinical and histomorphological description, see the following references.

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CHAPTER 11

Histiocytes

CHAPTER MENU

Langerhans Cell Histiocytoses (LCH)
Precursors of Langerhans Cell Histiocytoses
Langerhans Cell Histiocytoses
(Histiocytosis X)

Non-Langerhans Cell Histiocytoses
Proliferative
Granulomatous Storing
Hemophagocytic

PRECURSORS

Langerhans Cell Histiocytoses (LCH)

Langerhans cell histiocytoses are proliferative disorders of Langerhans cells, presenting with a wide spectrum of cutaneous and extracutaneous manifestations.

Precursors of Langerhans Cell Histiocytoses

The Langerhans cell (LHC) usually presents with characteristic morphological features: polygonal (histiocyte) silhouette, pale ample cytoplasm,

“coffee bean”-shaped nucleus; at the ultrastructural level, tennis racket-shaped Birbeck granules within the cytoplasm. Immunohistochemically, Langerhans cells express S100, CD1a, and Langerin (CD207). The latter is highly distinctive for Langerhans cells and allows differentiation from so-called indeterminate or veiled cells that are S100 positive, CD1a positive, Langerin (CD207) negative, and lack Birbeck granules.

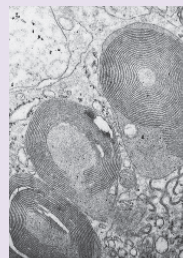
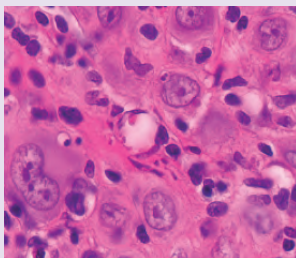
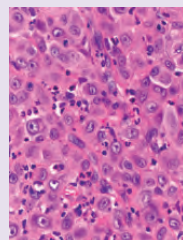
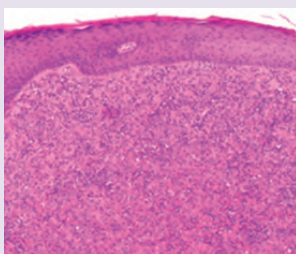
Congenital Self-healing Reticulohistiocytosis (Hashimoto–Pritzker)

Nodule on the heel of a baby* (left)

Dense granulomatous infiltrate (top mid and right)

Large histiocytic cells (bottom mid)

Concentric intracytoplasmatic lamellar bodies (bottom right)



*copyright: Bonifazi, E., R. Caputo, et al. (1982)

Cl: In newborns, multiple papules and nodules are found on the trunk, head, palms, and soles, occasionally with central ulceration. The children are otherwise healthy. As the lesions involute, they leave behind hypo- or hyperpigmented macules or patches.

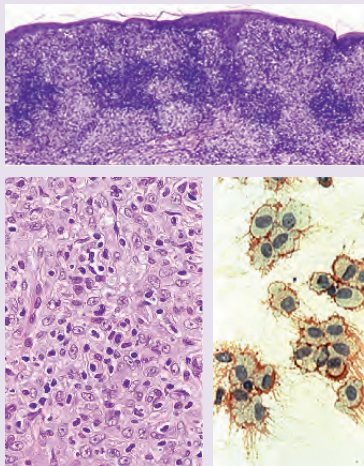
Hi: Dense proliferation of large histiocytic cells, which show characteristic intracellular concentric lamellae under the electron microscope. No Birbeck granules.

Indeterminate Cell Histiocytosis

Papules and
confluent plaques
(left)

Large
mononuclear
cells and foci
of lymphocytes
(right top and
bottom left)

Veiled cells in
culture (bottom
right)



Indeterminate cell histiocytosis (ICH) is a rare neoplastic disorder typified by the proliferation of indeterminate histiocytic cells, which are morphologically and immunophenotypically (CD1a+, S-100+) related to Langerhans cells but possess no Birbeck granules and are negative for Langerin (CD207).

Cl: Multiple asymptomatic red-brown papules and plaques on the trunk and limbs of adults.

Hi: Non-epidermotropic dermal infiltrate composed of mononuclear cells with abundant cytoplasm and prominent nuclei. These cells are so-called

veiled cells (S100+, CD1a+, Langerin negative). Concomitant lymphocytic infiltrate may simulate a pseudofollicular pattern under low power.

Langerhans Cell Histiocytoses (Histiocytosis X)

Class I: S100 positive, CD1a positive, Langerin (CD207) positive, Birbeck granules positive.

Occurs in several forms: proliferative (malignant Letterer–Siwe), storing (Hand–Schüller–Christian), granulomatous (eosinophilic granuloma). Affects various organs, including the skin.

Table 11.1 Langerhans cell histiocytoses and their characteristics.

Disease	Age	Skin involvement	Clinical features	Course	Prognosis
Letterer–Siwe	First years of life	~90–100%	Fever, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, bone lesions	Acute	Mortality rate: 50–66%
Hand–Schüller–Christian	Children, adults	~30%	Osteolytic bone lesions, diabetes insipidus, exophthalmos, otitis	Subacute to chronic	Mortality rate: <50%
Eosinophilic granuloma	Mainly adults	<10%	Solitary bone or skin lesions	Chronic	Favorable

Source: Kazakov, D., Burg, G., and Kempf, W. (2005) Langerhans cell histiocytosis (histiocytosis X). In: Burg, G. and Kempf, W. (eds) *Cutaneous Lymphomas*. Boca Raton: CRC Press.

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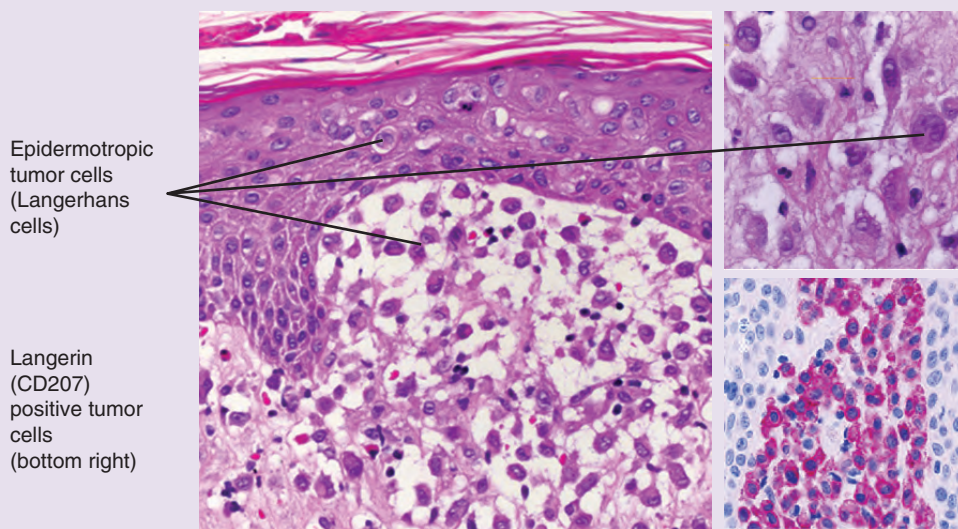
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Congenital Langerhans Cell Histiocytosis (Letterer–Siwe Disease)

Scaly crusty lesions in a child



Congenital Langerhans Cell Histiocytosis (Letterer–Siwe Disease)



CI: Skin lesions occur during the first year of life and are composed of tiny rose-pink or brownish-red, translucent papules and patches, which become scaly and crusted and may coalesce into plaques. Petechial and purpuric lesions, pustules, and vesicles as well as small erosions can also be seen. Predilection sites are the scalp and seborrheic sites such as the postauricular area, nasolabial folds, perioral region, and upper trunk. Additional symptoms include fever, weight loss, rash, lymphadenopathy, hepatosplenomegaly, pancytopenia, and purpura.

Hi:

- Superficial erosion and scale crust
- In the papillary dermis, band-like pale cell infiltrate with epidermotropism
- In the epidermis, prominent pagetoid spread of single cells or accumulation of Pautrier abscess-like intraepidermal cellular clusters
- Hallmark cell type: Langerhans cell with abundant amphophilic cytoplasm and coffee bean-shaped nucleus. Cells often have histiocytoid morphology
- Variable number of lymphocytes, plasma cells, eosinophils

- Immunohistochemical expression of S100, CD1a, Langerin (CD207)

Electron microscopy: Tennis racket-shaped Birbeck granules.

DD: Seborrheic dermatitis; other eczematous lesions; other forms of LCH.

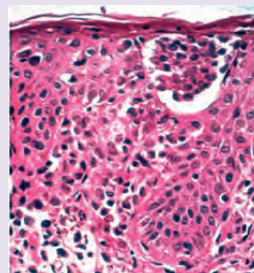
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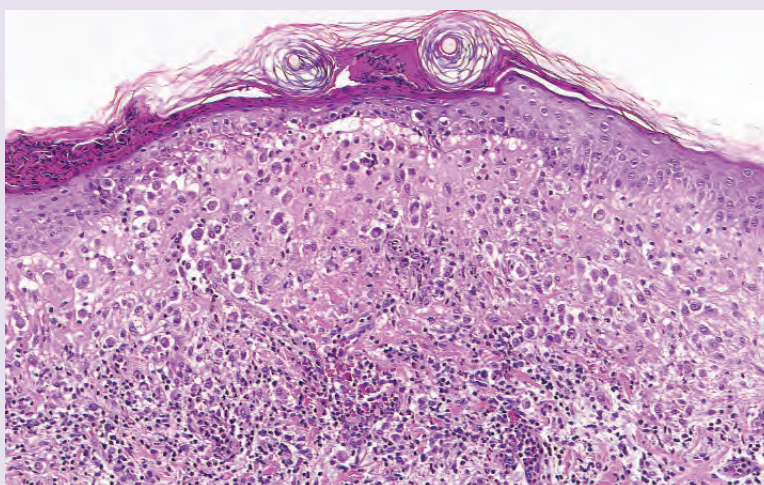
Hand-Schüller-Christian Adult LCH Histiocytosis

Intertriginous
eroded and
crusted
lesions (left)

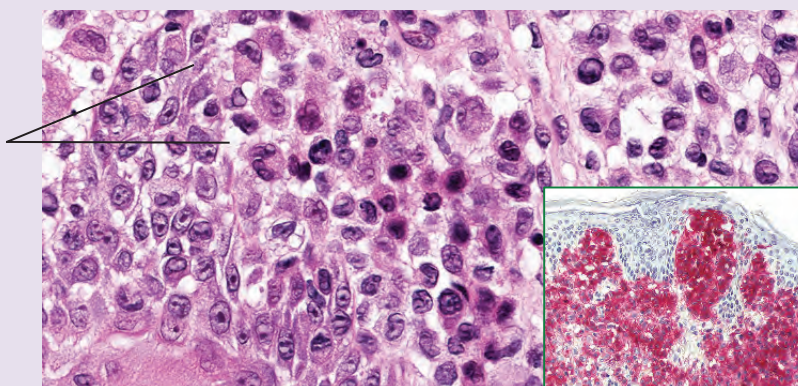
Intraepidermal
microabscess,
containing
Langerhans
cells
(right)



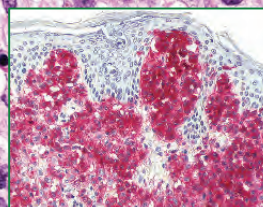
Epidermotropic
Langerhans
cell infiltrate in
the upper dermis



Intraepidermal
Langerhans
cells.



Inset: Langerin
positive
infiltrate
in the upper
dermis (right)



Cl: Skin lesions occur in about 30% of cases, preferentially in the large skinfolds in the perianal and inguinal area. The typical triad includes osteolytic skull lesions (100%), diabetes insipidus (50%), and exophthalmos (10%). Otitis media, generalized

lymphadenopathy, hepatosplenomegaly, and pulmonary disease may be additional findings.

Hi: The histological features are identical with those of Letterer-Siwe disease. In addition, some foamy cells may be present.

DD: Psoriasis; intertriginous eczema; candida mycosis.

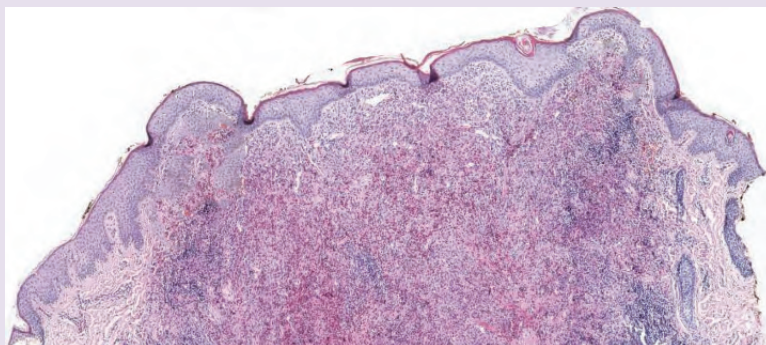
References

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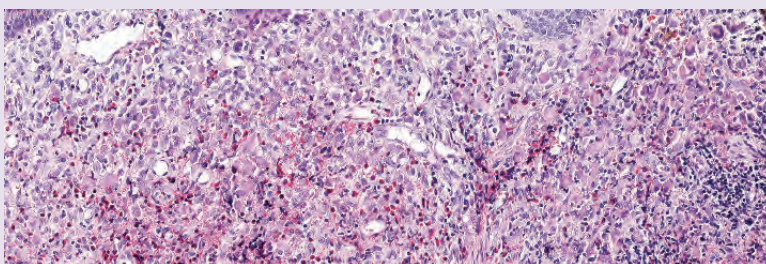
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Solitary Langerhans Cell Tumor (Eosinophilic Granuloma)

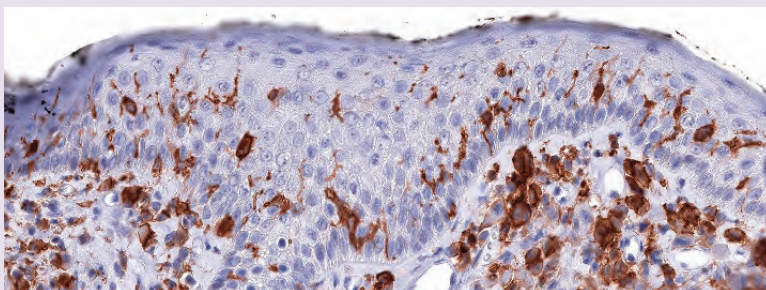
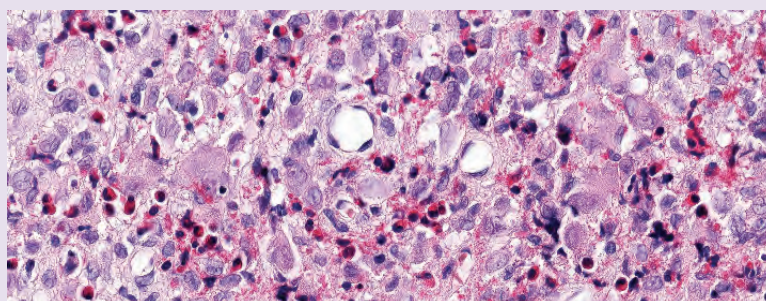
Nodular dermal infiltrate



Langerhans cells with intermingled eosinophils



CD1a-positive Langerhans cells



PROLIFERATIVE

Cl: The most common site of involvement is bone. Skin lesions are uncommon and present as deep dermal or subcutaneous nodules which are not clinically distinct.

Hi: Cellular mixed granulomatous infiltrate without necrosis, composed of large mononuclear cells with amphophilic eosinophilic cytoplasm (Langerhans cells), histiocytes, lymphocytes, and many eosinophils.

DD: Lesions with predominant eosinophilic infiltration: lymphomatoid papulosis; granuloma faciale; insect bite reaction; Wells syndrome.

References

Cambazard, F., Dezutter-Dambuyant, C., Staquet, M.J., Schmitt, D., and Thivolet, J. (1991) Eosinophilic granuloma of bone and biochemical demonstration

of 49-kDa CD1a molecule expression by Langerhans-cell histiocytosis. *Clin Exp Dermatol* **16**(5): 377–82.

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Non-Langerhans Cell Histiocytoses

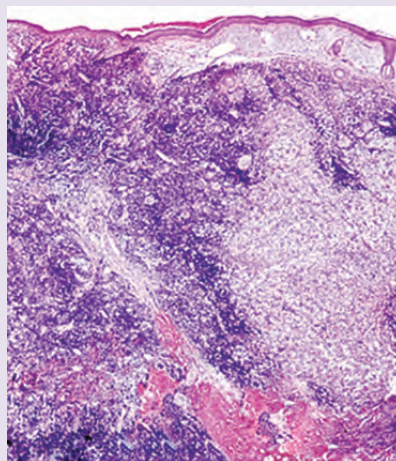
Class II: CD1a negative, Langerin (CD207) negative, Birbeck granule negative, S100 and histiocytic monocytic markers with variable expression (CD14, CD64, CD68, CD163).

Proliferative

Proliferative Histiocytoma (Progressive Nodular Histiocytosis, PNH)

Progressive nodular histiocytosis (face)

Foamy histiocytes, surrounded by lymphocytic infiltrate (right)



Cl: Multiple, slowly growing red-brown nodules with smooth surface in adults, preferentially involving the face and neck, increasing in number over time. No systemic or lymph node involvement.

Hi:

- Dermal infiltrates of foamy histiocytes
- Variants with spindled cells and large histiocytes with ample cytoplasm
- Lymphocytic infiltrate in the adjacent dermis

Immunohistochemistry: Histiomonocytic markers mostly positive (CD14, CD64, CD68, CD163).

DD: Cutaneous B-cell lymphoma; sinus histiocytosis.

References

Caputo, R., Brezzi, A., Vaccari, G., Cavicchini, S., and Gianotti, R. (2002) Progressive histiocytosis: description of a case of slow-course non-Langerhans cell histiocytosis. *Dermatology* **205**(3): 293–7;discussion 296–7.

Glavin, F.L., Chhatwall, H., and Karimi, K. (2009) Progressive nodular histiocytosis: a case report with literature review, and discussion of differential

PROLIFERATIVE

diagnosis and classification. *J Cutan Pathol* **36**(12): 1286–92.

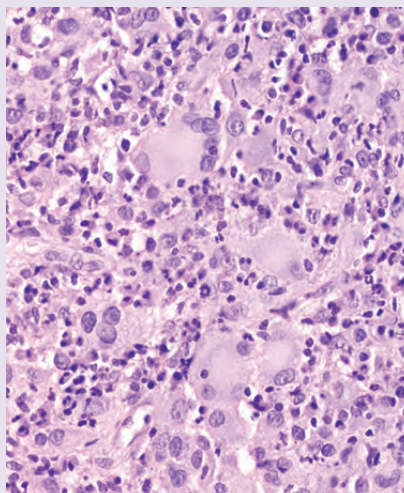
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Benign Cephalic Histiocytosis

Flat papules in the face, simulating flat warts

Histiocytes and multinucleated giant cells intermingled with lymphocytes (right)



Cl: Benign, self-healing, non-Langerhans cell proliferation of unknown cause affecting infants and children, which presents with multiple asymptomatic flat yellow to red-brown papules, confined to the head and neck area. Spontaneous regression after months and years.

Hi:

- The histological features are very similar to those seen in juvenile xanthogranuloma
- Large histiocytes with eosinophilic cytoplasm and multinucleated giant cells with lymphocytes in between
- Three variants:
 - papillary dermal
 - lichenoid
 - diffuse

Immunohistochemistry: S100 positive; CD1a negative.

Electron microscopy: No Birbeck granules.

DD: Plane warts; multiple juvenile xanthogranulomas; generalized eruptive histiocytomas.

References

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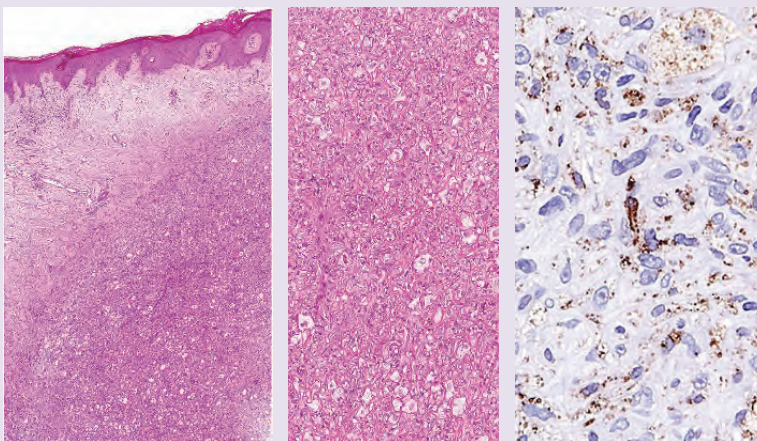
PROLIFERATIVE

**Multicentric Reticulohistiocytosis (Lipoid Dermatoarthritis)
(Solitary Reticulohistiocytoma)**

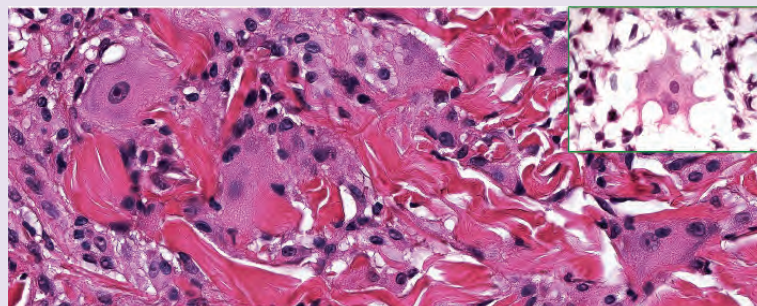
Nodular lesions
on the
interphalangeal
joints



Dense histiocytic
infiltrate with
scattered giant
cells (CD68+,
right)



Multinucleated
giant cells in
MRH; border
of the lesion



Cl: The disease typically affects women in their fourth or fifth decade. Small firm red-brown papules with smooth surface on the distal interphalangeal joints of the hands and on the ears. Rings of papules along the nailfolds. Mucosal involvement in 50% of patients. Association

with arthritis, immunological disorders, and malignancies.

Hi:

- Diffuse dermal infiltrate of oncocyctic histiocytes with ample eosinophilic, finely granular (“ground-glass”) cytoplasm and small round nuclei

PROLIFERATIVE

- Foamy histiocytes and lymphocytes
- Sudan black B fat stain and oil red O are positive
- Fibrosis in older lesions

DD: Reticulohistiocytosis; rheumatoid arthritis; gout; lipogranulomatosis of Farber.

References

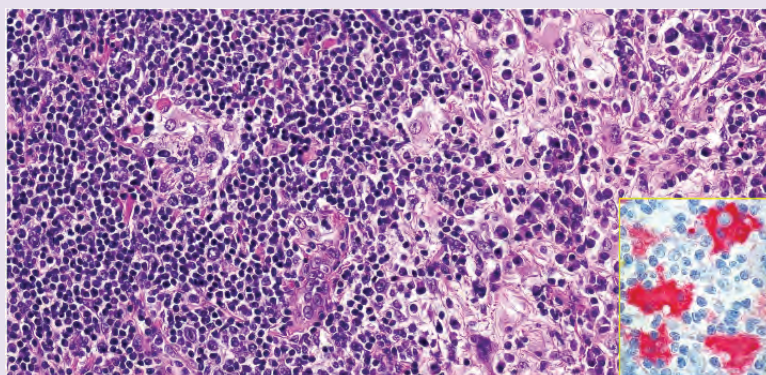
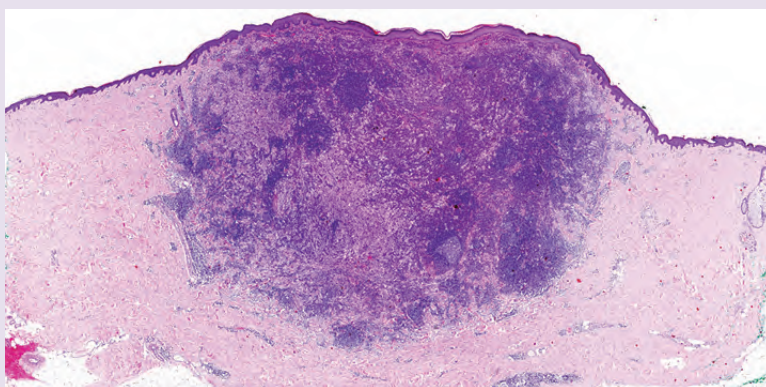
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Sinus Histiocytosis With Massive Lymphadenopathy

Small nodular lesions on the trunk



Strands and patches of dense lymphocytic infiltrate with scattered macrophages (mid and bottom). Inset: S100+ macrophages with phagocytosed lymphocytes (emperipolesis; beanbag sign)



GRANULOMATOUS STORING

Cl: Solitary or multiple cutaneous nodules imitating nevi or dermatofibromas. The lymph nodes are spared. The term *sinus histiocytosis with massive lymphadenopathy* is a misnomer which reflects the identical histomorphology of a probably unrelated reactive disorder in the lymph nodes (Rosai–Dorfman type of sinus histiocytosis). Cutaneous lesions generally are regarded to represent specific morphological variants of a histiocytic disorder.

Hi:

- Lymphoma-like diffuse cellular mixed infiltrate in the upper and mid dermis

- Mostly lymphocytes and plasma cells
- Hallmark cells are very large interspersed histiocytic cells (“fried eggs”) with ample cytoplasm and large vesicular nucleus. Within the cytoplasm, there are one or more phagocytosed (emperipolesis) lymphocytes or plasma cells
- Immunohistochemically, these cells are strongly positive for S100
- There may be intratumoral dilated lymphatics filled with lymphocytes and plasma cells

Granulomatous Storing

Juvenile Xanthogranuloma (Nevoxanthoendothelioma; Xanthoma Multiplex; Juvenile Giant Cell Granuloma)

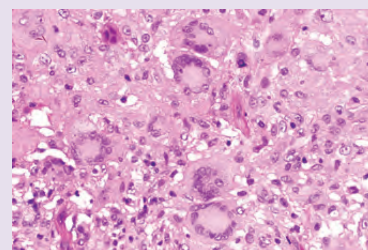
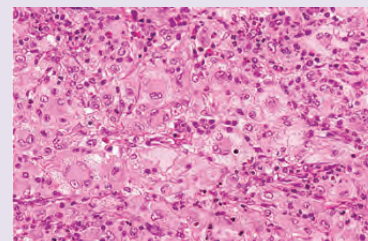
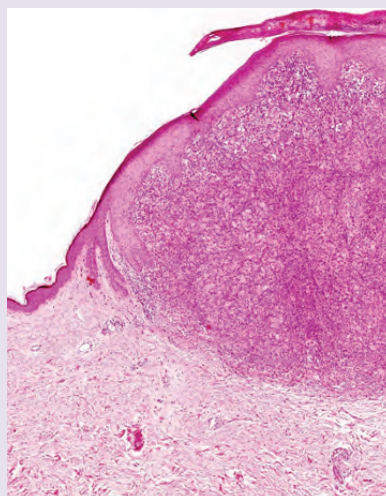
Slightly red
early lesion (left)

Yellowish
mature
nodule (right)

Histiocytic
nodular
infiltrate
without grenz
zone (“touching
the epidermis”)
(left)

Foamy
histiocytes and
macrophages
(top right)

Touton giant cells
(bottom right)



GRANULOMATOUS STORING

Juvenile xanthogranuloma (JXG) is a benign, self-limited histiocytic disorder of unknown cause, predominantly affecting infants and children, but also seen in adults.

CI: Solitary, sometimes multiple yellow-brown papules with smooth surface, preferentially in the head and neck area of white children, with a tendency to spontaneous regression over a period of months or years. Extracutaneous involvement affects the eye and internal organs.

Hi:

- Early lesion: moderately dense perivascular and interstitial infiltrate composed mainly of medium-sized histiocytes with oval or irregular nuclei and eosinophilic, granular cytoplasm
- Fully evolved lesion:
 - Well-circumscribed nodular dermal infiltrate
 - The infiltrate lacks a grenz zone and completely fills the papillary dermis, even in early stages of the lesion
 - Histiocytes with foamy, eosinophilic or vacuolated cytoplasm
 - Multinucleated giant cells of the Touton type
 - Concomitant mixed inflammatory infiltrate of lymphocytes and eosinophils
 - Spindle cell variants and morphological overlap with dermatofibroma exist
 - Fibrosis in resolving lesions

Immunohistochemistry: Variable expression of CD14, CD64, CD68, and CD163. S100 protein often positive, particularly in lesions rich in phagocytosing cells and neutrophils; CD1a negative.

DD: Xanthoma (disseminatum); mastocytoma; Spitz nevus; eruptive histiocytoma.

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Xanthoma Disseminatum



Eruptive xanthomas



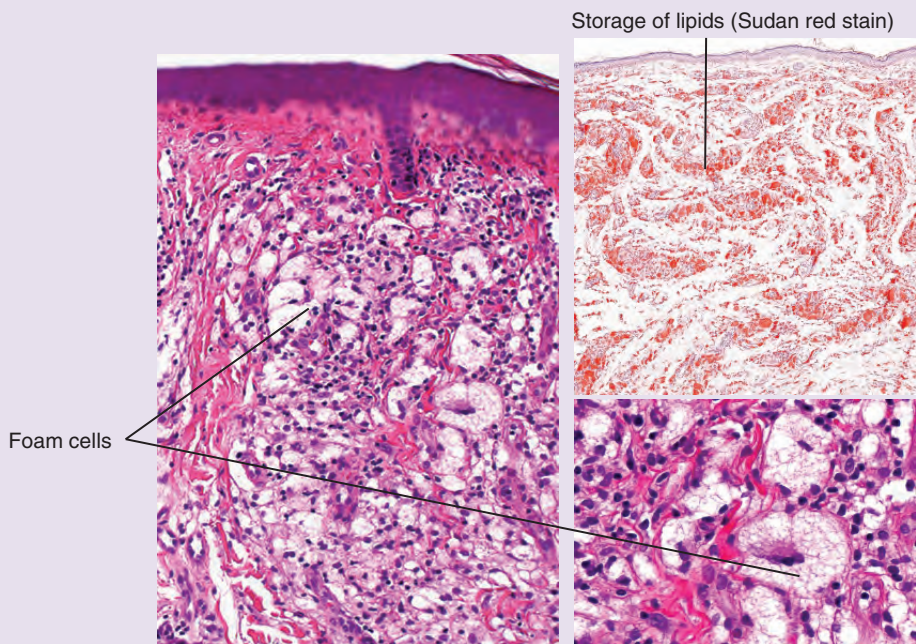
Nodular xanthomas



Tendinous xanthomas

GRANULOMATOUS STORING

Xanthoma Disseminatum



Cl: Multiple yellowish papules and plaques are found on the eyelids, joints, and flexural areas of the extremities, axillae, groin, face (eyelids), perianal region, and trunk. Frequent association with diabetes insipidus and hyperlipoproteinemia.

Hi:

- Foamy histiocytes amidst a monocytic-histiocytic infiltrate in the reticular dermis
- Characteristic granuloma annulare-like pattern with foamy histiocytes near the center
- Histiocytes show broad, pale, foamy, fat-containing cytoplasm (Sudan red stain) and small, roundish, regular nuclei
- Concomitant inflammatory infiltrate with lymphocytes, neutrophils, and eosinophils

Immunohistochemistry: Expression of histiocytic markers (CD14, CD68, CD163); S100 and CD1a negative. Hallmark marker is adipophilin which detects intracytoplasmic lipids.

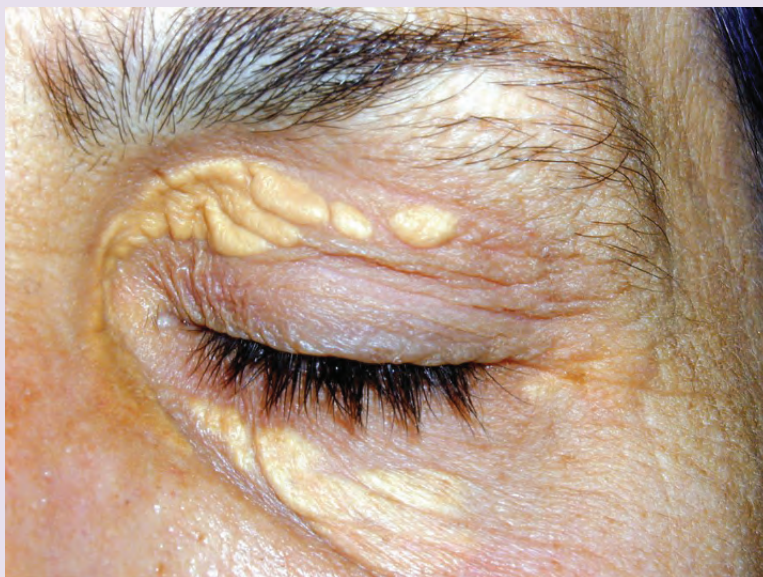
DD: Juvenile xanthogranuloma; eruptive histiocytoma; benign cephalic histiocytosis.

References

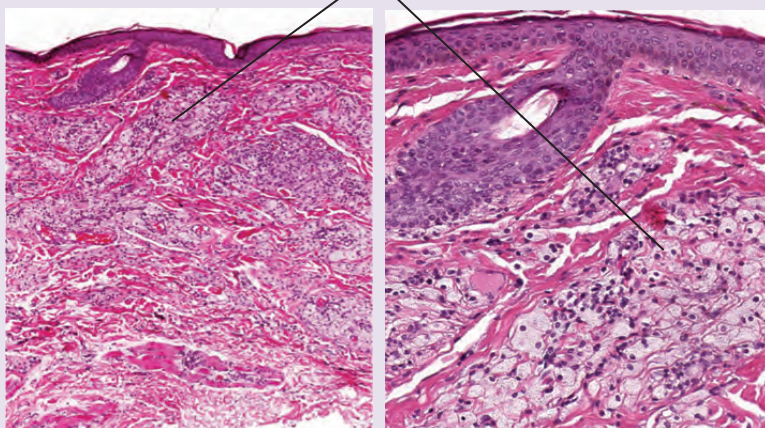
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GRANULOMATOUS STORING**Xanthelasma Palpebrarum**

Yellow plaques



Foam cells



Cl: Yellowish plaques, preferentially on the eyelids.

Hi: In the reticular dermis there are lobular aggregates of foam cells, which are macrophages filled with lipids.

DD: Xanthoma.

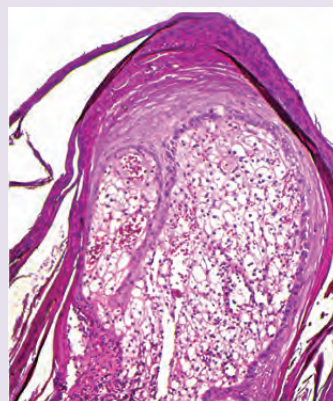
References

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GRANULOMATOUS STORING

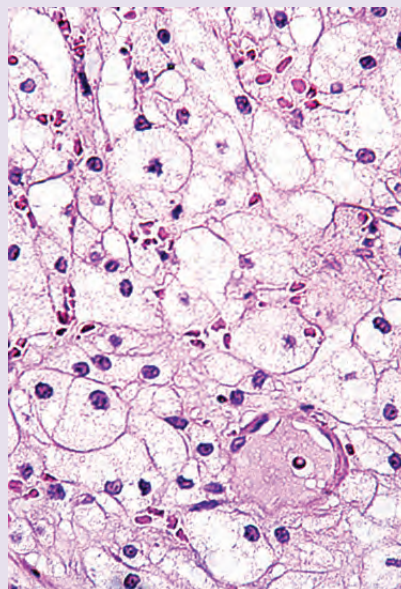
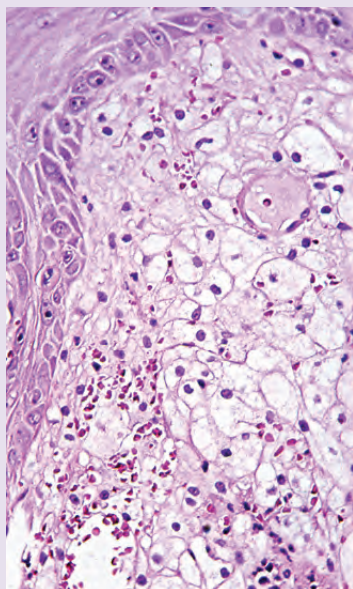
Verruciform Xanthoma

Verruciform
nodule on
the tongue



Filiform lesion (nose)

Foam cells



Cl: Typical localisation is the oral mucosa but anogenital, nasal mucosa and other sites may be involved, showing a yellow-red filiform or papillomatous lesion. Much larger and confluent lesions with identical histomorphology may be encountered in CHILD nevus (females) and CHILD mosaicism (males), the latter lesions being much smaller and wart-like.

Hi:

- Verrucous and markedly acanthotic epithelial hyperplasia with elongation of the rete ridges

- Multifocal funnel-shaped eosinophilic keratinous columns within the epidermis (“wart on fire”)
- Accumulation of foamy histiocytes and macrophages loaded with lipids, filling the papillary dermis
- Fat-storing histiocytes strongly express adipophilin and histiocytic markers

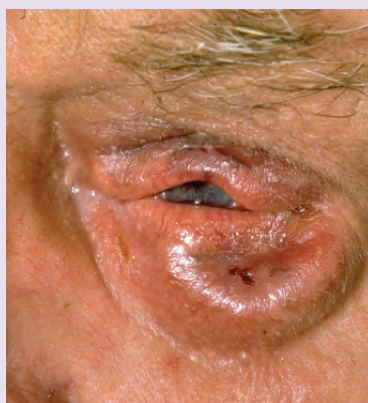
DD: Verruca vulgaris; squamous cell carcinoma.

References

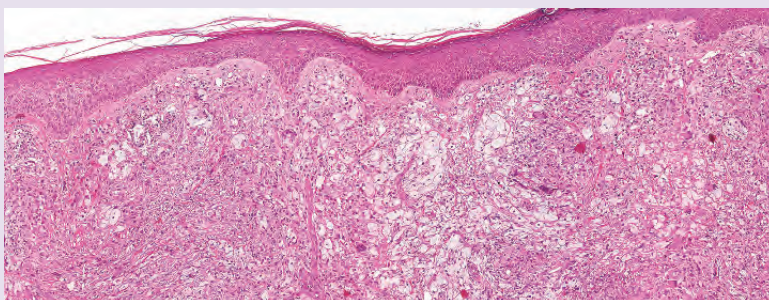
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Necrobiotic Xanthogranuloma (with Paraproteinemia)

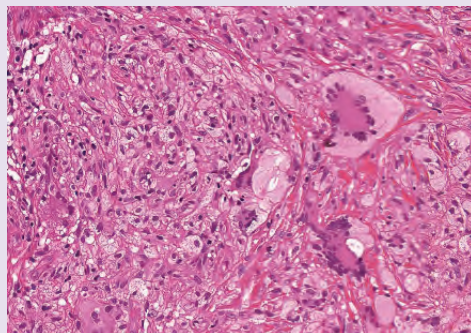
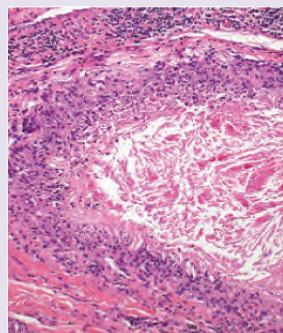
Infiltrated plaques on the trunk (left) and suborbital (right)



Foam cells (mid) with Touton giant cells (bottom right)



Palisading pattern with granulomatous border around necrosis and cholesterol deposits (left)



Cl: Yellow-red indurated nodules or plaques preferentially in the periorbital region and upper trunk. Often central depression. Association with paraproteinemia.

Hi:

- Early: dense histiocytic infiltrate with many plasma cells, often imitating diffuse type of granuloma annulare
- Late: large palisaded granulomatous lesion ("giant granuloma annulare")
- Large focal necrosis with stellate cholesterol clefts
- Foamy macrophages and exceedingly large multinucleate Touton-type giant cells
- Many plasma cells
- Sometimes marked lymphocytic infiltrate with germinal centers

DD: Xanthelasma; diffuse normolipemic plane xanthoma; granuloma annulare; necrobiosis lipoidica; sarcoidosis.

References

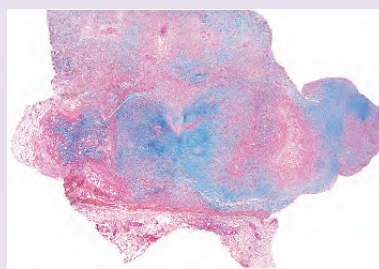
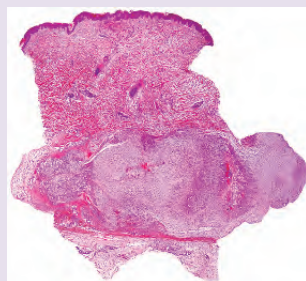
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Hereditary Progressive Mucinous Histiocytosis

Diffuse swelling;
chin, hand, finger

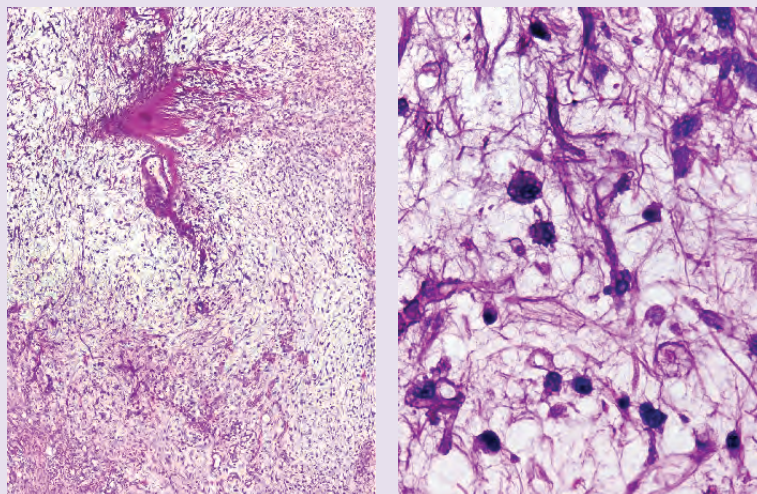


Mucinous material
in the deep dermis;
alcian blue (right)



Hereditary Progressive Mucinous Histiocytosis

Mucinous stroma
(left) with large
histiocytes (right)



* Courtesy of L Requena, Madrid

This disease is considered to be a rare familial form of eruptive histiocytoma with prominent mucinosis.

Cl: Slowly progressive inherited disease presenting with plaques or papules, mostly starting in childhood or young adulthood. Temporary spontaneous regression. No extracutaneous involvement. No involvement of mucous membranes.

Hi:

- Epidermis not affected
- Well-circumscribed unencapsulated aggregates of histiocytes with abundant mucin (alcian blue) in the mid or deep dermis
- Scattered large epithelioid histiocytes with bizarre nuclei (CD68 and lysozyme positive; S100/CD1a and F XIIIa negative)
- No inflammation
- Few mast cells

Electron microscopy: Myelin bodies and zebra bodies but no Birbeck granules.

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Hemophagocytic Familial Hemophagocytic Lymphohistiocytosis

Extremely rare fatal disease showing macrophagocytic infiltrates with hemophagocytosis in several organs and rarely also involving the skin.

HEMOPHAGOCYTIC

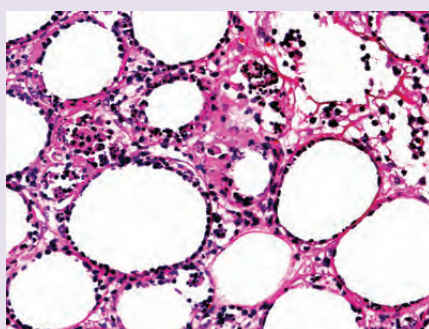
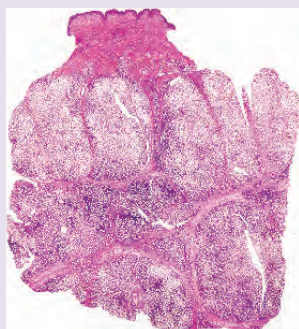
References

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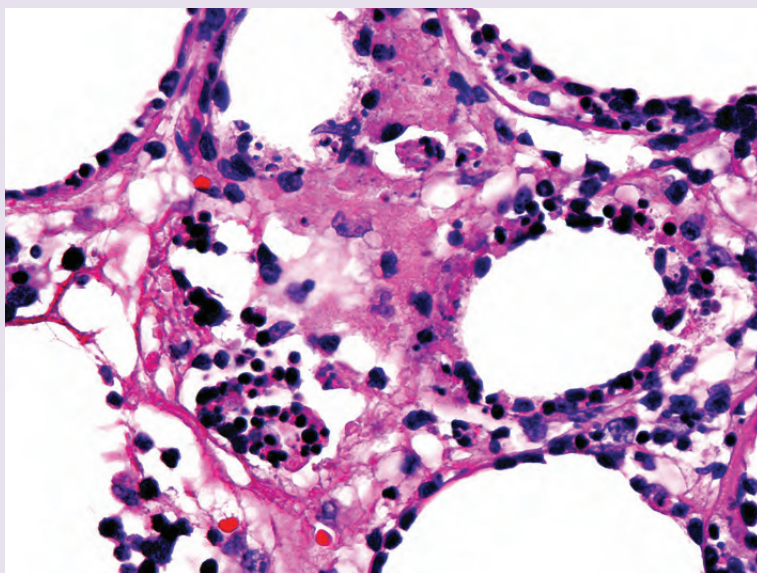
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Histiocytic Cytophagic Panniculitis

Lobular panniculitis



Necrobiosis and macrophages containing phagocytised cells ("beanbag cells"). Karyorrhexis



Cl: Clinical aspect of deep-seated panniculitis with moderate overlying erythema. May occur at any site.

Hi:

- Mostly lobular cellular panniculitis, with infiltrate spilling over into the septa
- Mixed infiltrate, containing many histiocytes, macrophages, and multinucleate cells

- Hallmark cells are large histiocytic phagocytosing multinucleate cells (bean-bag cells) with intracytoplasmic lymphocytes
- No "rimming" of CD8-positive T-suppressor cells
- Immunophenotypically, histiocytes (CD68, CD163) predominate
- Negative for CD30 and CD56

CHAPTER 12

Hematopoietic Disorders

CHAPTER MENU

Lymphoid Skin Infiltrates	Cutaneous Mature B-Cell Lymphoid Neoplasms (CBCL)
Cytomorphology, Major Cell Types	Cutaneous Marginal Zone B-Cell Lymphoma (MZL; MALT Type)
Pattern of Small Cell Lymphocytic Infiltrates	Primary Cutaneous Follicle Center Lymphoma (FCL)
Pseudolymphoma (PL)	Diffuse Large B-Cell Lymphoma (DLBCL)
Nodular B-Cell PL	Cutaneous Spindle B-Cell Lymphoma
Nodular T-Cell PL	Extracutaneous B-Cell Lymphoma (BCL) with Frequent Skin Involvement
Pseudo-Mycosis Fungoides (Mycosis Fungoides Simulators)	Intravascular Lymphomas
Cutaneous Mature T-Cell Lymphoid Neoplasms (CTCL)	Intravascular Large B-Cell Lymphoma (IV-LBCL) (Systemic Angioendotheliomatosis)
Mycosis Fungoides, Classic Alibert–Bazin Type	Intravascular T Cell Lymphoma
Simulators and Variants of Mycosis Fungoides: “Parapsoriasis”	Secondary Skin Involvement in Leukemias/Lymphomas
Granulomatous Slack Skin	Chronic Lymphocytic Leukemia (CLL)
Pagetoid Reticulosis (PR), Unilesional (Woringer–Kolopp)	Myeloid and Monocytic Leukemias
Sézary Syndrome (SS)	T-Zone Lymphoma
CD30-Positive Lymphoproliferative Disorders (LPD) of the Skin	Adult T-Cell Leukemia/Lymphoma (ATLL)
Subcutaneous Panniculitis-Like Lymphoma	Immature Hematopoietic Malignancies
Primary Cutaneous Peripheral Lymphoma (PTL), Unspecified (NOS)	Blastic Plasmacytoid Dendritic Cell Neoplasm
Extranodal NK/T-Cell Lymphoma, Nasal Type (Subcutaneous)	Precursor Lymphoblastic Leukemia/Lymphoma
Angioimmunoblastic T-Cell Lymphoma	

Some disorders formerly referred to as malignant proliferations of “histiocytes” or “mononuclear phagocytes” in fact turned out to be large cell lymphoproliferative disorders and will be discussed in this chapter.

Lymphoid Skin Infiltrates

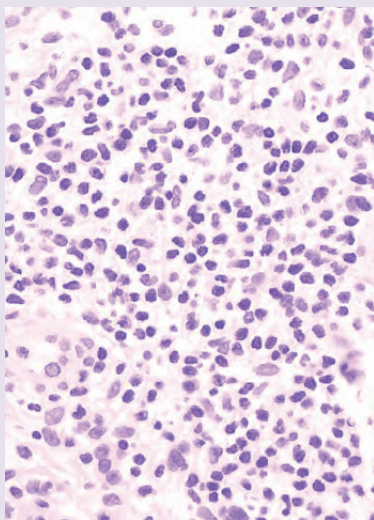
The skin provides distinct homing conditions for lymphoid cells, which depend on the homing behavior of the cells themselves due to different surface molecules and cytokines released on one side and the composition and structure of target tissue where the cells tend to settle and proliferate. Lymphocytic infiltrates can be distinguished by their growth pattern, the cytomorphology of the neoplastic cells and their phenotypes.

In routine hematoxylin-eosin staining, small T-cell and B-cell infiltrates and their subtypes can be roughly differentiated due to the distinct cytomorphology of cells and the histological compartment of skin, presenting as T-cell and B-cell patterns respectively. A *diffuse growth pattern* extending between collagen bundles is found in large T-cell or B-cell lymphomas. Pseudolymphomatous infiltrates also may present a distinct pattern (see Pseudolymphomas, below). An *interstitial growth* is very typical for myelomonocytic skin infiltrates. These prototypes of growth pattern of hematopoietic cells in the skin can provide preliminary cyto- and histogenetic information which must be supplemented and confirmed by additional clinical, immunological, and molecular findings.

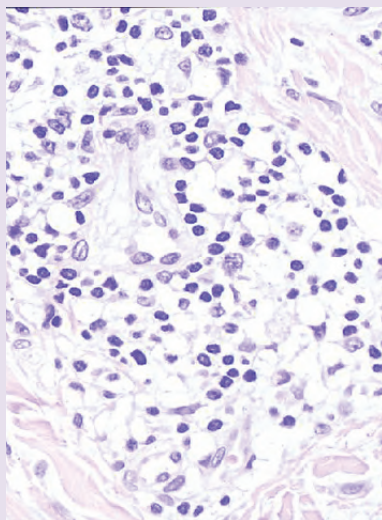
CYTOMORPHOLOGY

Cytomorphology, Major Cell Types

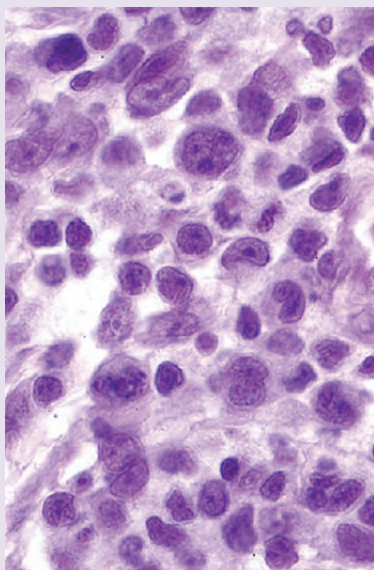
T-Cells



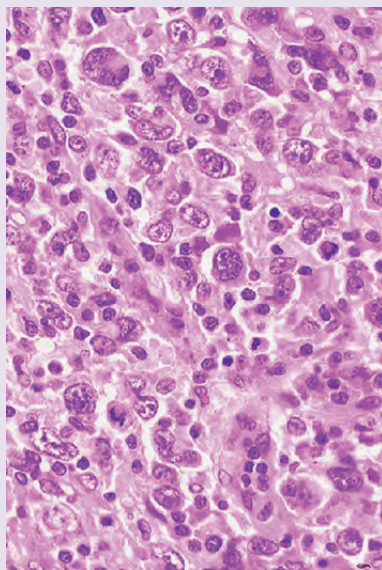
Cerebriform T-cells



Small pleomorphic T-cells



Pleomorphic large T-cells



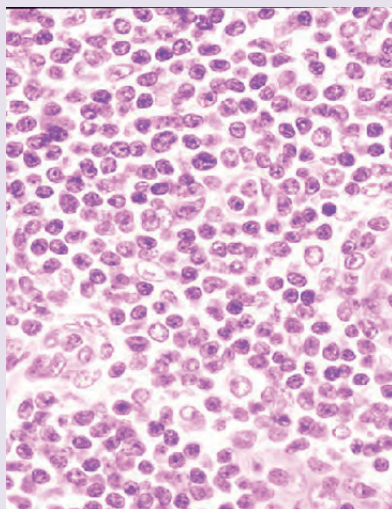
Anaplastic T-cells

- Small cerebriform T-cells
- Small pleomorphic T-cells

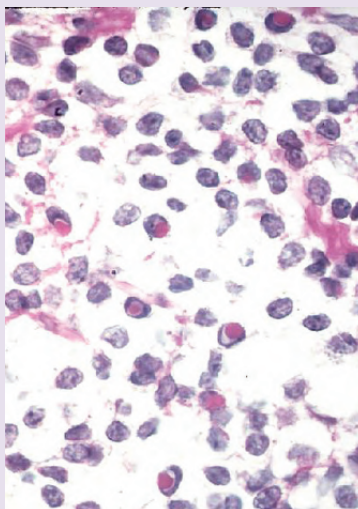
- Pleomorphic large T-cells
- Anaplastic T-cells

CYTOMORPHOLOGY

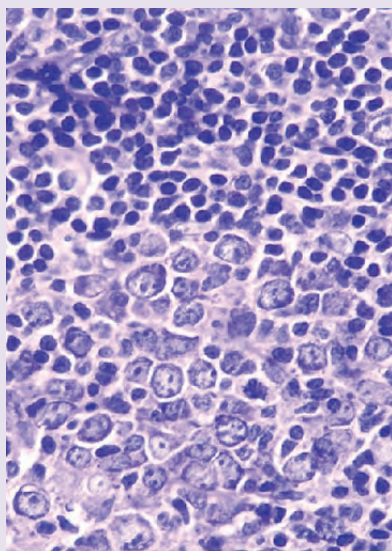
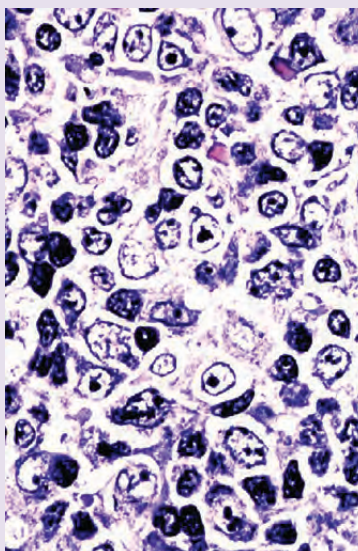
B-Cells



Small lymphocytic B-cells



Lymphoplasmacytoid B-cells

Centrocytic (top, small) and
centroblastic (bottom, large)
B-cells

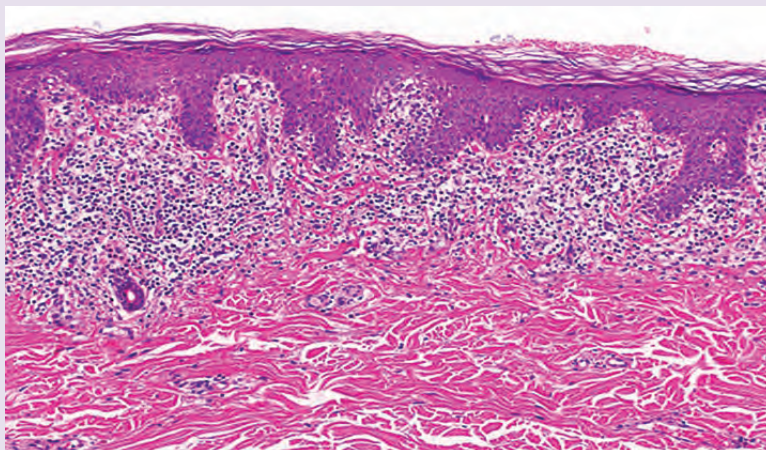
Immunoblastic B-cells

- Small lymphocytic B-cells
- Small lymphoplasmacytoid B-cells
- Small/medium-sized cleaved follicle center cells (centrocytes)
- Large non-cleaved follicle center cells (centroblasts)
- Large immunoblastic B-cells

PATTERN

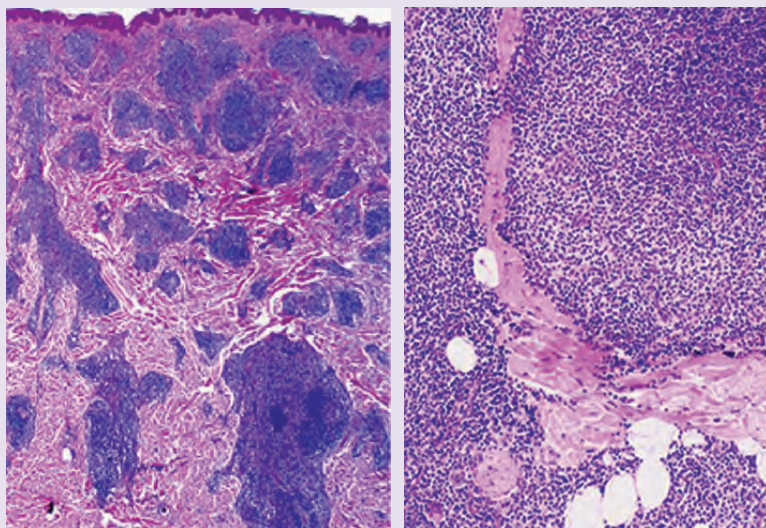
Pattern of Small Cell Lymphocytic Infiltrates

T-Cell Pattern



- Upper dermis
- Band-like epidermotropic infiltrate with single cells or clusters of lymphoid cells in the epidermis (Pautrier microabscesses)
- Infiltrate in the papillary dermis; cells are loosely packed due to edema in the dermis
- Edema in the papillary dermis, sometimes simulating a free “grenz zone,” transforming into fibrosis
- Infiltration along adnexal structures
- Prominent postcapillary venules

B-Cell Pattern



NODULAR B-CELL PL

- Mid and deep dermis, perivascular rather than periadnexal
- Nodular, compact, well-circumscribed lymphocytic infiltrates
- Well-defined concave borders of the infiltrates
- Cells are densely packed without intercellular edema
- “Grenz zone”; no epidermotropism

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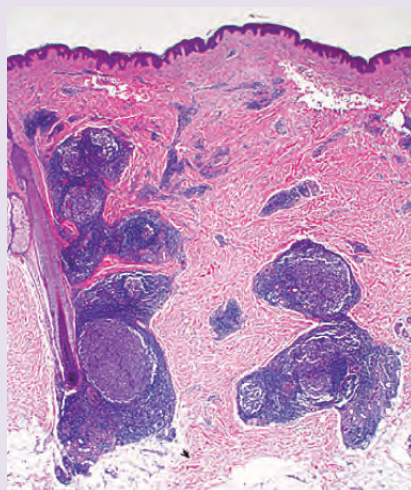
Pseudolymphoma (PL)

Nodular B-Cell PL

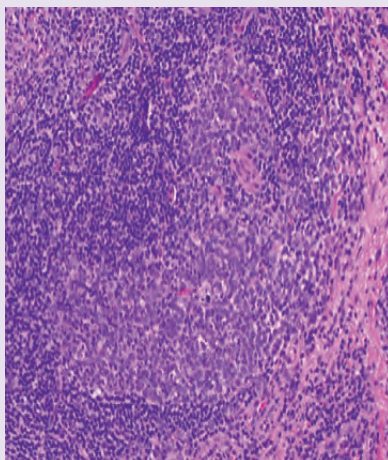
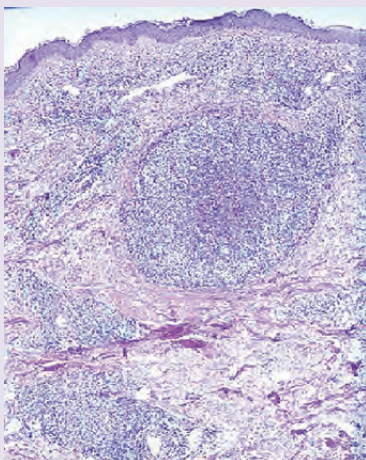
Lymphadenosis Cutis Benigna (Lymphocytoma Cutis)

Pseudolymphomatous swelling of the concha of the ear (left)

“Follicular” infiltrates (right)

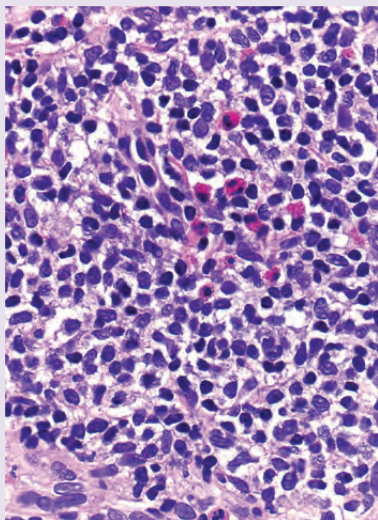


Germinal center formation (left) with starry sky macrophages (right)

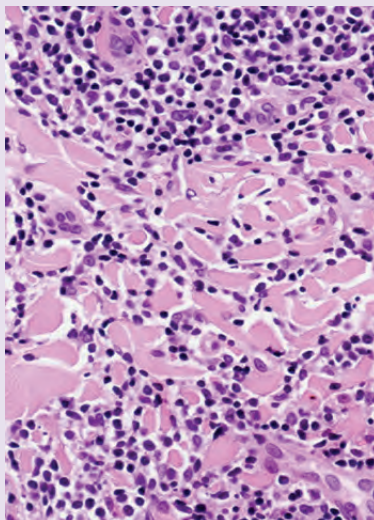


NODULAR B-CELL PL

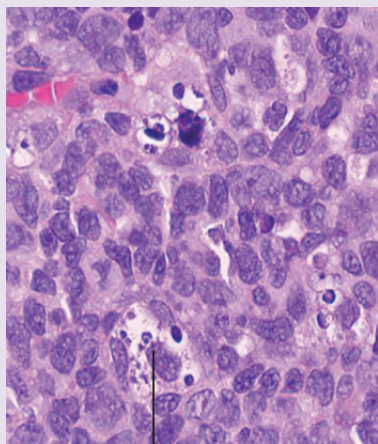
Lymphadenosis Cutis Benigna (Lymphocytoma Cutis)



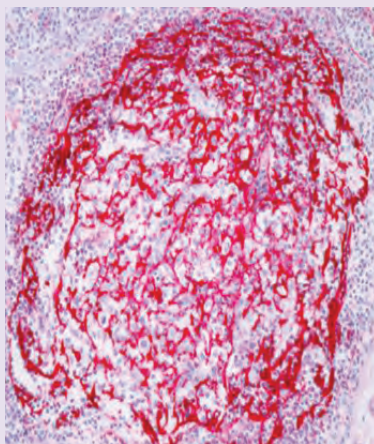
Lymphocytes and eosinophils
in the interfollicular area (left)



Indian file-like distribution of
lymphocytes between collagen bundles



Starry sky macrophage with
tingible bodies



Regular network of
CD21+ follicular dendritic cells

In Europe, this is most commonly caused by infection with *Borrelia burgdorferi* after a tick bite (*Ixodes ricinus*), but also by other microbiological, physical or chemical agents. In the United States and other parts of the world, *Borrelia burgdorferi* DNA in cutaneous B-cell lymphomas or pseudolymphomas is absent.

Giant follicular forms of lymphadenosis benigna cutis with "inverted follicular pattern" (dark chromatin in the center and clear border zone) today are regarded as marginal zone B-cell lymphomas.

Cl: Mostly solitary, rarely multiple, disseminated soft red nodules on the head, preferentially on the ear lobes. Other predilections are the nose, nipples, inguinal area, and scrotum.

Hi:

- Nodular dermal infiltrates, located in the upper and mid dermis, but may extend into the deep dermis
- Reactive lymph follicles with macrophages containing ingested nuclear material (Fleming's tingible body macrophages) within the follicles, producing a "starry sky" pattern

- Small lymphocytes surrounding the reactive lymph follicles and large follicle center cells (centroblasts)
- Interfollicular area composed of small B-cells, loosely arranged small T-cells, histiocytes and some eosinophils and plasma cells, spreading between collagen bundles and rendering the border less well demarcated than in cutaneous B-cell lymphoma, in which the border is convex and sharply demarcated

Immunophenotype: Polyclonal B-lymphocytic infiltrate (CD20; CD79a) without immunoglobulin (Ig) heavy or light chain restriction; however,

monotypic expression of kappa or lambda chains can be identified in some cases. Regular and sharply demarcated network of CD21+ follicular dendritic cells in the reactive lymph follicles. Lymphocytes expressing T-cell markers in the interfollicular areas.

DD: Marginal zone lymphoma and follicle center lymphoma.

Differentiation between B-Pseudolymphoma (PL) and Cutaneous B-Cell Lymphoma (CBCL)

	CBCL	PL
Clinical features		
Number of lesions	Solitary or multiple	Usually solitary
Extracutaneous involvement	Possible	Absent
Recurrences	Likely	Unusual
Survival time	Affected	Not affected
Histological features		
Pattern of infiltrate	Diffuse or nodular, "bottom-heavy"	Nodular (>90%), "top-heavy"
Additional cells	Usually absent	Eosinophils, plasma cells
Transformation	May occur	Never occurs
Border of the infiltrate	Sharply demarcated, concave	Lacerated, convex
Immunophenotype		
Immunoglobulin light chains	Monotypic	Polytypic expression (kappa or lambda)
B-cell marker expressing cells	>50% cells	≤50% cells
T-cell marker expressing cells	Few	>50% cells
CD21-positive dendritic cells	Mostly absent or grossly irregular pattern	Mostly present, regular pattern
Genotype		
Ig heavy chain rearrangement	Present in most cases	Absent in most cases

References

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Colli, C., Leinweber, B., Mullegger, R., Chott, A., Kerl, H., and Cerroni, L. (2004) *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. *J Cutan Pathol* **31**(3): 232–40.

Duncan, S.C., Evans, H.L., and Winkelmann, R.K. (1980) Large cell lymphocytoma. *Arch Dermatol* **116**(10): 1142–6.

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Moulouguet, I., Ghnassia, M., Molina, T., and Fraitag, S. (2012) Miliarial-type perifollicular B-cell pseudolymphoma (lymphocytoma cutis): a misleading eruption in two women. *J Cutan Pathol* **39**(11): 1016–21.

Nakayama, H., Mihara, M., and Shimao, S. (1987) Malignant transformation of lymphadenosis benigna cutis: a possibly transformed case and B-cell lymphoma. *J Dermatol* **14**(3): 266–9.

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NODULAR T-CELL PL

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Watanabe, R., Nanko, H., and Fukuda, S. (2006) Lymphocytoma cutis due to pierced earrings. *J Cutan Pathol* **33**(Suppl 2): 16–19.

Wood, G.S., Kamath, N.V., Guitart, J., et al. (2001) Absence of *Borrelia burgdorferi* DNA in cutaneous B-cell lymphomas from the United States. *J Cutan Pathol* **28**(10): 502–7.

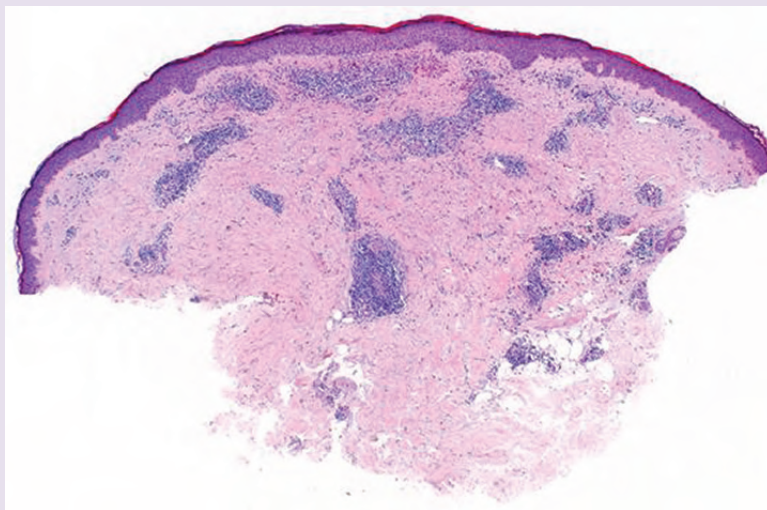
Nodular T-Cell PL

CD30+ Pseudolymphoma in Scabies

Scabies in a child.
Inset: mite



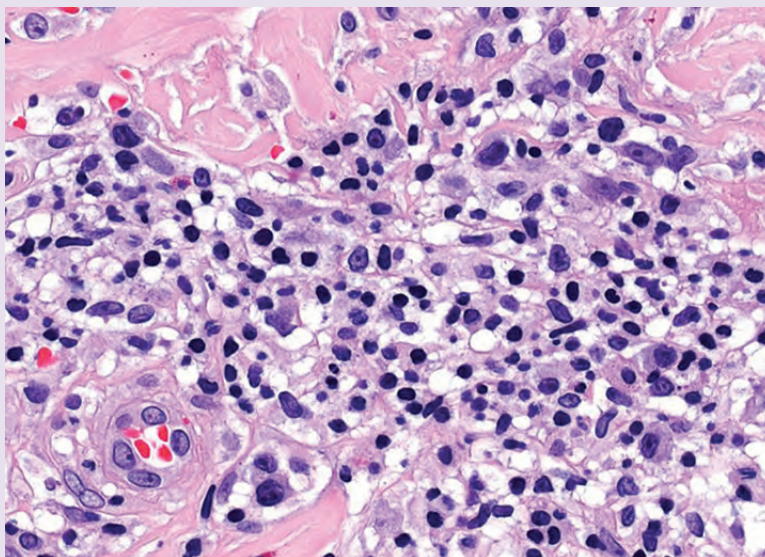
Patchy dermal infiltrate in a
wedge-shaped
distribution



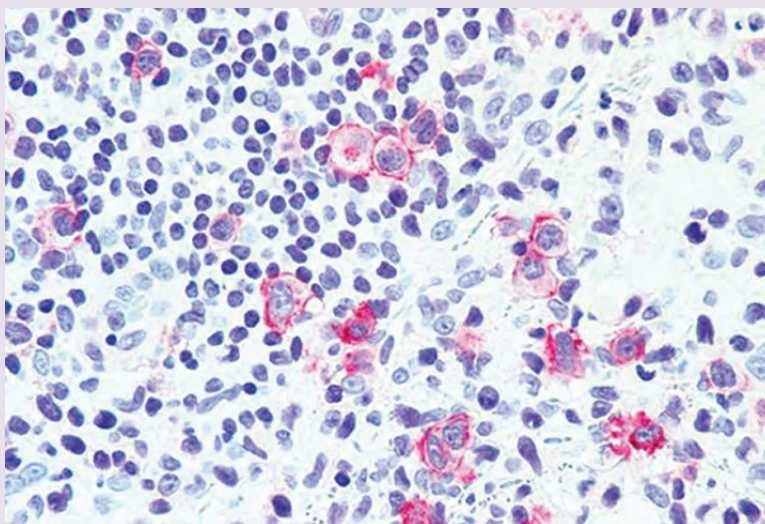
NODULAR T-CELL PL

CD30+ Pseudolymphoma in Scabies

Small
lymphocytes
and large
pleomorphic
cells



Large
pleomorphic
cells, CD30+



Cl: Nodular lesion at the site of a tick bite,

Hi: Wedge-shaped infiltrate composed of activated polyclonal T helper cells (CD3+, CD4+) and admixture of a few medium-sized to large activated CD30+ T-cells; some eosinophils.

References

- Gallardo, E., Barranco, C., Toll, A., and Pujol, R.M. (2002) CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis. *J Cutan Pathol* **29**(6): 368–73.
- Guitart, J. and Hurt, M.A. (1999). Pleomorphic T-cell infiltrate associated with molluscum contagiosum. *Am J Dermatopathol* **21**(2): 178–80.
- Kempf, W. (2006) CD30+ lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. *J Cutan Pathol* **33**(Suppl 1): 58–70.
- McCalmont, T.H. and LeBoit, P.E. (2000) A lymphomatoid papule, but not lymphomatoid papulosis! *Am J Dermatopathol* **22**(2): 188–90.

NODULAR T-CELL PL

Papular (Secondary) Syphilis

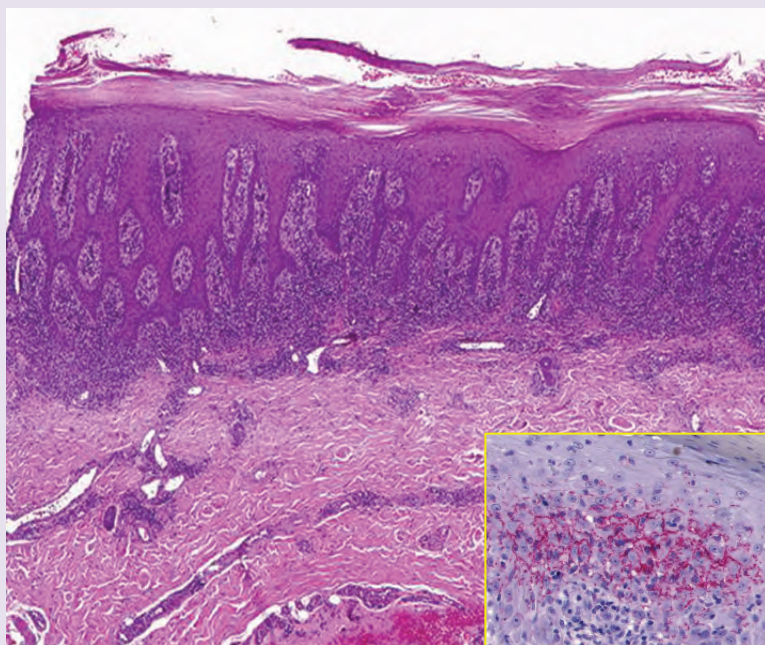
Papulosquamous lesions on the trunk and in the face



Dense infiltrate in the papillary dermis

Lymphohistiocytic dermal perivascular infiltrate (left)

Treponema pallidum immunostaining (inset)



CI: In late-stage secondary syphilis (>2 years after infection, without treatment), disseminated small papules and papulosquamous lesions may appear on head, trunk, and extremities, including mucous membranes, presenting as plaques and patches on the palms and soles or as condyloma-like lesions in the anogenital region.

Hi:

- Interface dermatitis

- Superficial and deep perivascular and interstitial infiltrate
- Lymphocytes and histiocytes with scattered eosinophils and many plasma cells
- Occasionally granulomatous features
- In early stages of secondary syphilis, spirochetes may be detected using Warthin–Starry stain

DD: Lymphomatoid papulosis; tick bites.

PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)

References

- Hoang, M.P., High, W.A., and Molberg, K.H. (2004) Secondary syphilis: a histologic and immunohistochemical evaluation. *J Cutan Pathol* **31**(9): 595–9.
- Park, J.H. and Kim, Y.C. (2013) Secondary syphilis with numerous eosinophils. *J Cutan Pathol* **40**(12): 1063–4.
- Pichardo, R.O., Lu, D., Sanguenza, O.P., and Tucker, R. (2002) What is your diagnosis? Secondary syphilis. *Am J Dermatopathol* **24**(6): 503–4.
- Rysgaard, C., Alexander, E., and Swick, B.L. (2014) Nodular secondary syphilis with associated

granulomatous inflammation: case report and literature review. *J Cutan Pathol* **41**(4): 370–9.

Pseudo-Mycosis Fungoides (Mycosis Fungoides Simulators)

Reference

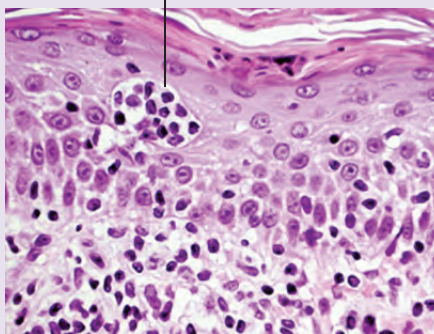
- Massone, C., Kodama, K., Kerl, H., and Cerroni, L. (2005). Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. *Am J Surg Pathol* **29**(4): 550–60.

Lymphomatoid Contact Dermatitis

Contact dermatitis against nickel (left)



Pautrier-like spongiotic vesicle



Cl: Red macules and papules in the area of contact with the allergen (chromium, nickel, other) and surroundings.

Hi:

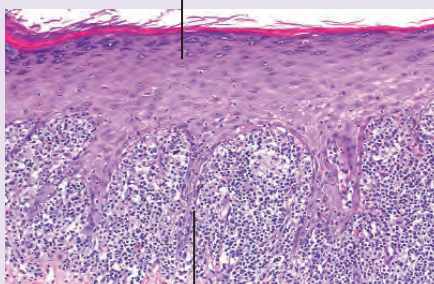
- Acanthosis, spongiosis
- Lymphohistiocytic infiltrate in the upper dermis
- Epidermotropism of single cells or of clusters of lymphocytes, forming Pautrier-like intraepidermal microabscesses
- Eosinophils may be present
- Edema, followed by fibrosis in the upper dermis
- Prominent postcapillary venules

Lichen Planus

Flat papules (left)



Hypergranulosis



Sawtooth-like elongation of rete ridges

PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)

Cl: Small papules with whitish smooth surface and Wickham stripes preferentially on the wrist of the arm.

Hi:

- Interface dermatitis
- Acanthosis, sawtooth-like elongation of rete ridges
- V-shaped hypergranulosis, hyperkeratosis

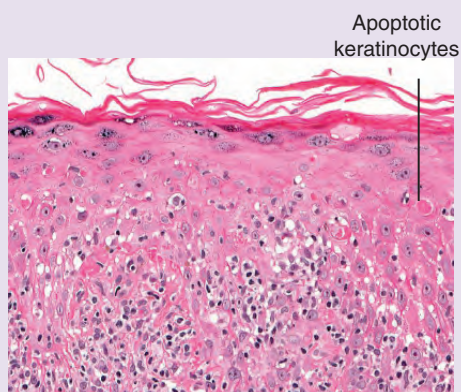
- Subepidermal band-like lymphocytic infiltrate
- *Caveat:* rare cases may harbor clonal T-cells

Reference

Schiller, P.I., Flaig, M.J., Puchta, U., Kind, P., and Sander, C.A. (2000) Detection of clonal T cells in lichen planus. *Arch Dermatol Res* **292**(11): 568–9.

Drug Reactions

Red-bluish well circumscribed plaques (left)



Lichenoid interface dermatitis

Cl: Fixed drug reactions present as well-circumscribed red-brown macular lesion(s).

Hi:

- Very similar to lichen planus, but usually larger number of eosinophils
- Apoptotic keratinocytes
- Extravasation of erythrocytes

Early Vitiligo

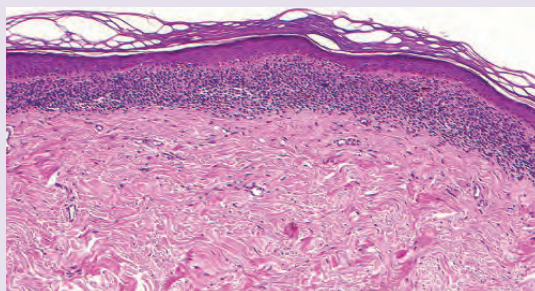
Band-like subepidermal infiltrate, simulating patch-stage mycosis fungoides, may be found at the active border of vitiligo.

Lichen Sclerosus et Atrophicus

Whitish atrophic plaques on the trunk (left)



Epidermal atrophy. Band-like lymphocytic infiltrate in the upper dermis (right)



PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)

Cl: Whitish atrophic plaques; occasional intracutaneous bleeding, especially in the genital area.

Hi: In early lesions, there is interface dermatitis and lymphocytic infiltrate in the papillary dermis. Later lesions develop prominent subepidermal edema and hyalinized connective tissue overlying the lymphocytic infiltrate.

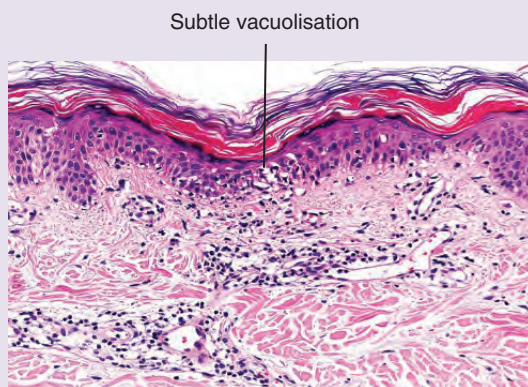
Reference

Citarella, L., Massone, C., Kerl, H., and Cerroni, L. (2003) Lichen sclerosus with histopathologic features simulating early mycosis fungoides. *Am J Dermatopathol* **25**(6): 463–5.

Pityriasis Lichenoides Chronica

Small scaly maculo-papular lesions (left)

Predominantly lymphocytic epidermotropic infiltrate (right)



Cl: Disseminated red scaly maculopapular lesions.

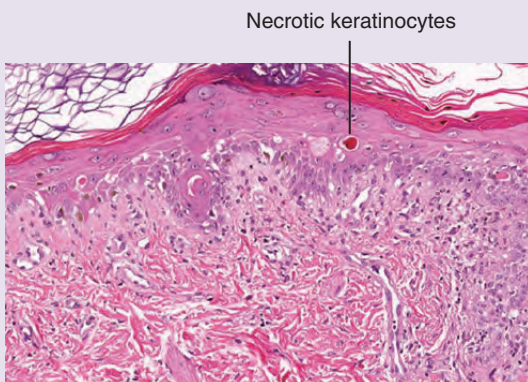
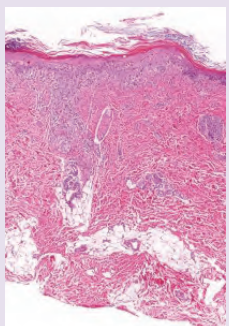
Hi: Focal vacuolisation, spongiosis, hyperparakeratosis with inclusions of neutrophils,

wedge-shaped superficial and deep predominant perivascular lymphocytic infiltrate.

Graft Versus Host Reaction (Acute)

Interface dermatitis (left)

Necrotic keratinocytes (right)



Cl: Maculopapular exanthema.

Hi: Similar to toxic epidermolytic necrolysis (TEN).

- Thinned epidermis
- Numerous apoptotic keratinocytes

- Satellite cell necrosis
- Vacuolar change at the dermoepidermal junction
- Scattered lymphocytic infiltrate in the papillary dermis

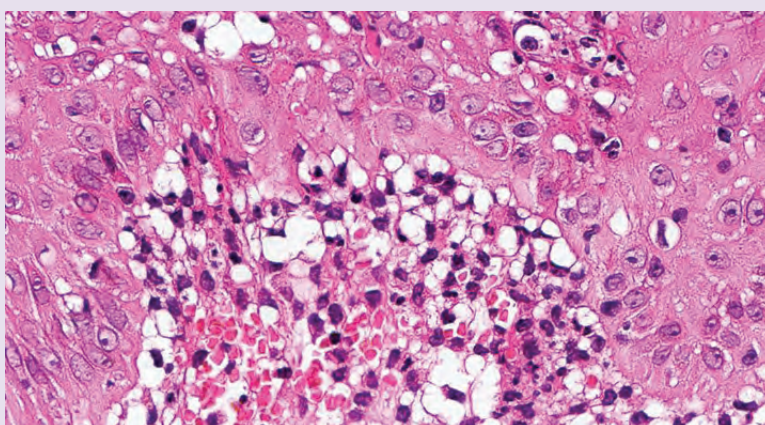
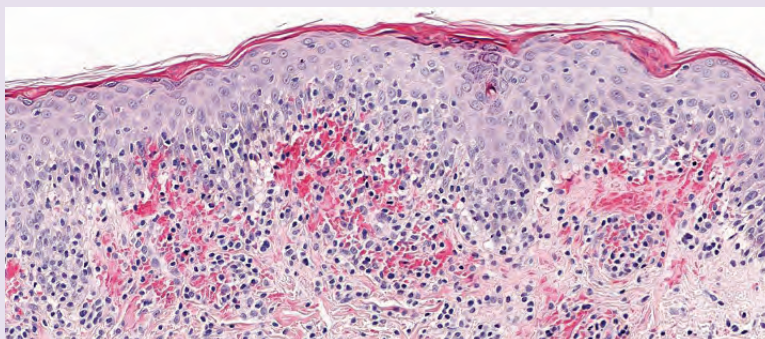
PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)

Pityriasis Lichenoides et Varioliformis Acuta (PLEVA)

Maculopapular lesions with necrotic crusted center, covered by small scales



Interface dermatitis and extravasation of erythrocytes (mid and bottom)



Cl: Preferentially in children, disseminated red scaly maculopapular lesions with necrotic center and crust formation are found. The disease regresses spontaneously within two years or earlier.

Hi:

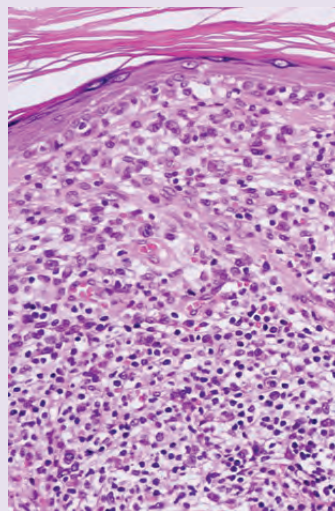
- Necrotic keratinocytes
- Interface dermatitis, edema
- Lymphocytes in the papillary dermis, some showing epidermotropism
- Erythrocyte extravasation and erythrocytes in the epidermis

PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)**Pigmented Purpuric Dermatitis (Lichen Aureus)**

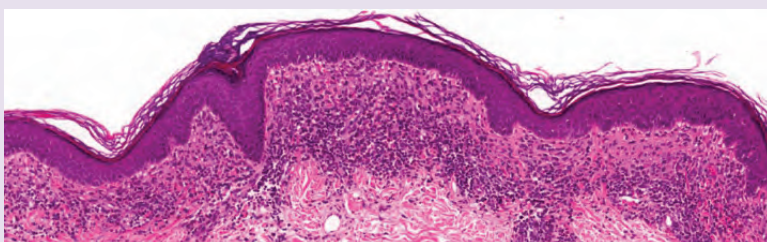
Bizarre purpuric pigmented lesions on the finger and on the foot (left top and bottom)



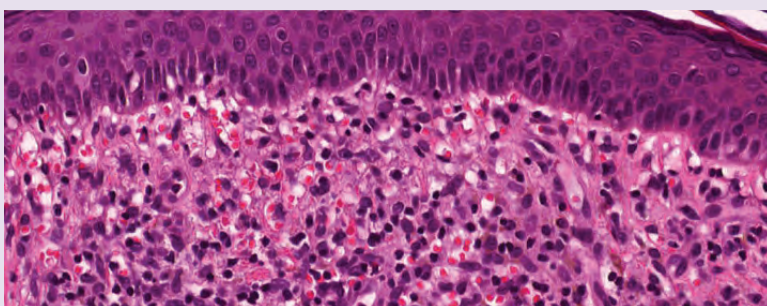
Atrophy of the epidermis. Epidermotropic lymphoid infiltrate in the upper dermis (right)



Band-like lymphocytic infiltrate in the upper dermis.



Vacuolisation of the dermo-epidermal junction, lymphocytes and erythrocyte extravasation.



Cl: Red-brown macular lesion(s).

Hi:

- Band-like infiltrate
- vacuolisation of the dermoepidermal junction

- Extravasated erythrocytes
- Deposits of hemosiderin (iron stain)

DD: Kaposi's sarcoma (clinically); cutaneous T-cell lymphoma; lichen planus.

PSEUDO-MYCOSIS FUNGOIDES (MYCOSIS FUNGOIDES SIMULATORS)

References

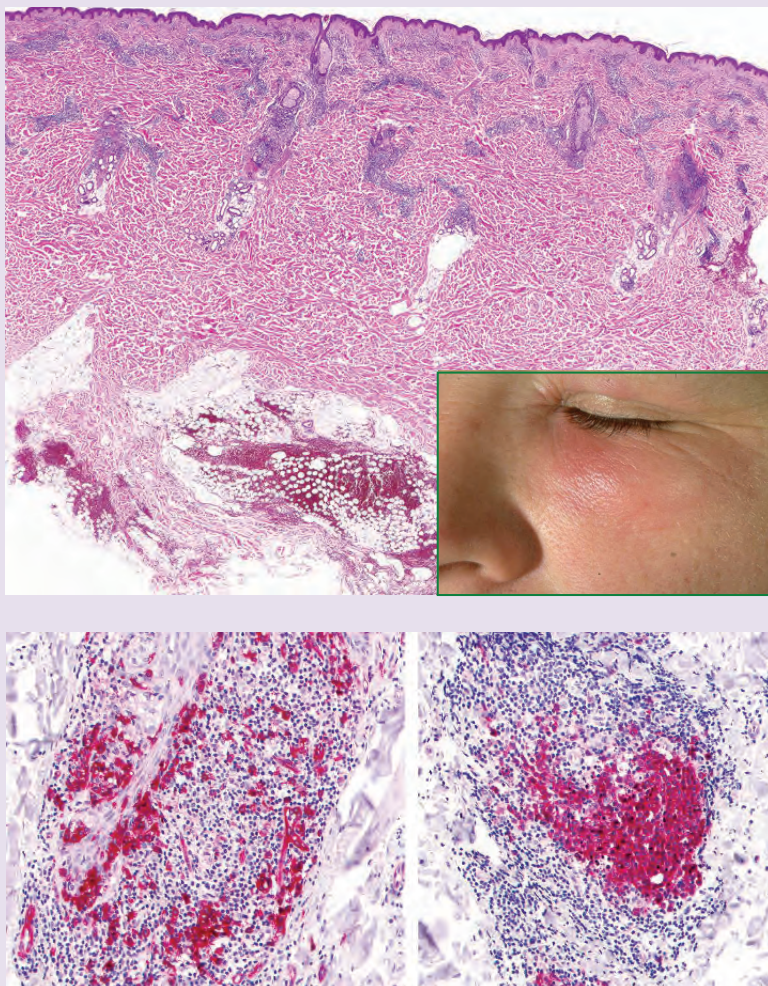
- Macquarrie, E.K., Pasternak, S., Torok, M., Veerassamy, S., and Walsh, N.M. (2011) Persistent pigmented purpuric dermatitis: granulomatous variant. *J Cutan Pathol* **38**(12): 979–83.
- Smoller, B.R. and Kamel, O.W. (1991) Pigmented purpuric eruptions: immunopathologic studies supportive of a common immunophenotype. *J Cutan Pathol* **18**(6): 423–7.
- Toro, J.R., Sander, C.A., and LeBoit, P.E. (1997) Persistent pigmented purpuric dermatitis and mycosis fungoides: simulant, precursor, or both? A study by light microscopy and molecular methods. *Am J Dermatopathol* **19**(2): 108–18.

Lymphocytic Infiltration Jessner–Kanof

Perivascular and periadnexial lymphocytic infiltrates in the upper and mid dermis

Inset:
Erythematous swelling suborbital

Patchy lymphocytic infiltrates with CD 123-positive plasmacytoid dendritic cells



Although the original presentation by Jessner and Kanof emphasized that the eruption is not due to drugs, most cases seem to be induced by drugs or food ingredients.

CI: According to the original description, the lesions are “flat, discoid, more or less elevated,

pinkish to reddish brown ... sometimes showing a circinate arrangement ... They disappear without sequelae and may return ... These cases must be distinguished particularly from ... drug eruption.” The face is the area of predilection.

MYCOSIS FUNGOIDES

Hi:

- Normal epidermis
- Patchy well-circumscribed polyclonal lymphocytic infiltrates in the upper and mid dermis, perivascular and periadnexal
- Predominantly T-cells but B-cells are also present

DD: Other pseudolymphomatous reactions; lupus erythematosus; acute contact dermatitis.

References

- Facchetti, F., Boden, G., de Wolf-Peeters, C., Vandaele, R., Degreef, H., and Desmet, V.J. (1990) Plasmacytoid monocytes in Jessner's lymphocytic infiltration of the skin. *Am J Dermatopathol* **12**(4): 363–9.
- Jessner, M. and Kanof, N.B. (1953) Lymphocytic infiltration of the skin. *Arch Dermatol* **68**: 447–9.
- Kuo, T.T., Lo, S.K., and Chan, H.L. (1994) Immunohistochemical analysis of dermal mononuclear cell infiltrates in cutaneous lupus erythematosus, polymorphous light eruption, lymphocytic infiltration of Jessner, and cutaneous lymphoid hyperplasia: a comparative differential study. *J Cutan Pathol* **21**(5): 430–6.
- Toonstra, J., and van der Putte, S.C. (1991) Plasmacytoid monocytes in Jessner's lymphocytic infiltration of the skin. A valuable clue for the diagnosis. *Am J Dermatopathol* **13**(4): 321–8.
- Weyers, W., Bonczkowitz, M., and Weyers, I. (1998) LE or not LE – that is the question: an unsuccessful attempt to separate lymphocytic infiltration from the spectrum of discoid lupus erythematosus. *Am J Dermatopathol* **20**(3): 225–32.

Cutaneous Mature T-Cell Lymphoid Neoplasms (CTCL)

Mycosis Fungoides, Classic Alibert–Bazin Type

Mycosis fungoides (MF) is the most common peripheral cutaneous T-cell lymphoma, initially and preferentially presenting in the skin and showing distinct clinical, histological (except in early stages), immunophenotypical, and genotypical features. It is slowly progressive over years and decades, developing stepwise through three clinical stages: patch stage, plaque stage, and tumor stage. Transformation into large cell lymphoma and extracutaneous spread may occur in the final stage of the disease. Besides the classic form of MF, there are many variants, presenting as erythrodermic, hypo- and hyperpigmented, follicular, granulomatous, bullous, hyperkeratotic, palmoplantar, ichthyosiform, and other forms.

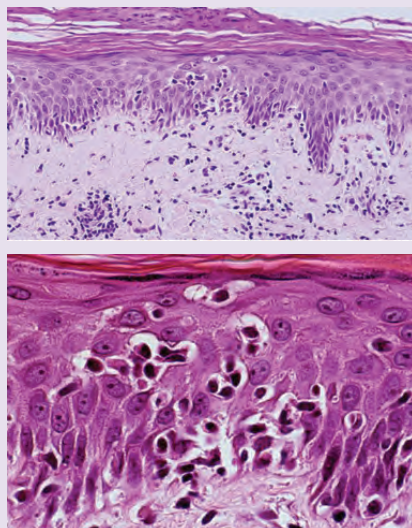
Reference

- Kazakov, D.V., Burg, G., and Kempf, W. (2004) Clinicopathological spectrum of mycosis fungoides. *J Eur Acad Dermatol Venereol* **18**(4): 397–415.

Mycosis Fungoides Patch Stage I

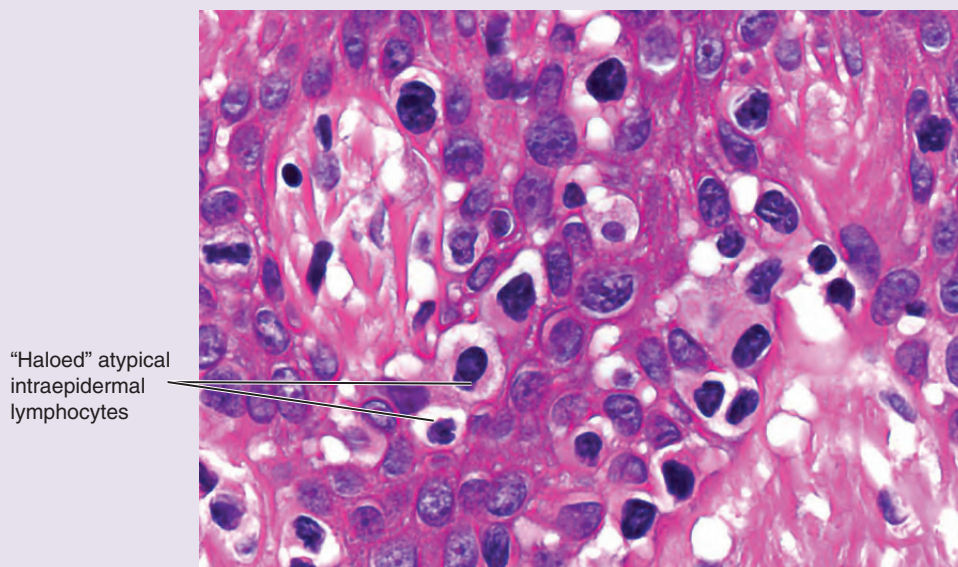
Patches on the trunk (left)

Epidermotropic infiltrate (right top and bottom)



MYCOSIS FUNGOIDES

Mycosis Fungoides Patch Stage I



The diagnosis of mycosis fungoides in early patch stage is one of the most challenging difficulties in dermatopathology. Many inflammatory conditions showing interface dermatitis, epidermotropism of lymphoid cells and prominent postcapillary venules can simulate patch-stage MF. Additional clinical and/or molecular information and long-term clinical follow-up are needed to make a correct diagnosis.

Cl: Multiple non-specific eczematous patches with no or subtle scaling, resembling chronic eczema, chronic superficial dermatitis ("parapsoriasis") or tinea corporis.

Hi: Differentiation of the non-specific lesions from superficial dermatitis may be difficult or impossible.

- Epidermis normal or slightly hyperkeratotic; no spongiosis
- Slight edema and small lymphocytes in the papillary dermis

- Lymphocytes (more than three in a row) in the basal layer of the epidermis, especially at the tips of the rete ridges

DD: Chronic (atopic) dermatitis; parapsoriasis; superficial fungal infection.

References

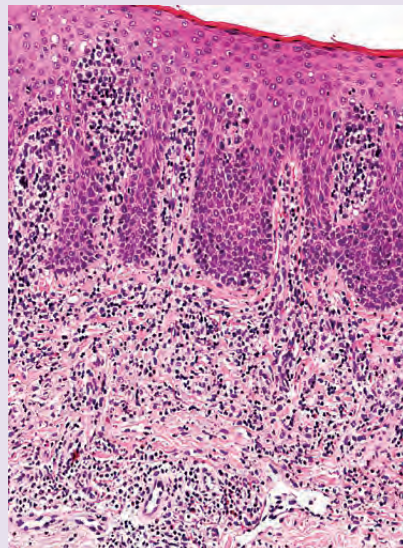
- Massone, C., Kodama, K., Kerl, H., and Cerroni, L. (2005) Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. *Am J Surg Pathol* **29**(4): 550–60.
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MYCOSIS FUNGOIDES**Mycosis Fungoides Plaque Stage II (CD4+; CD8-)**

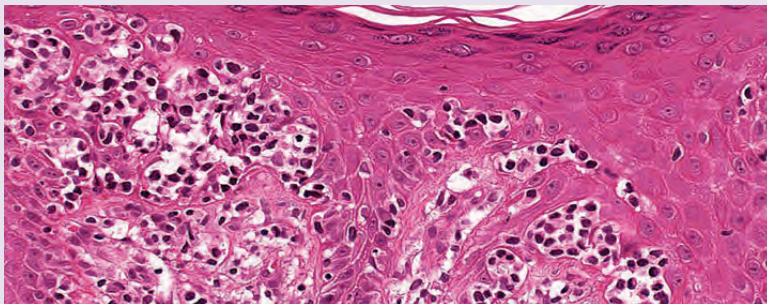
Plaques on the trunk (left)



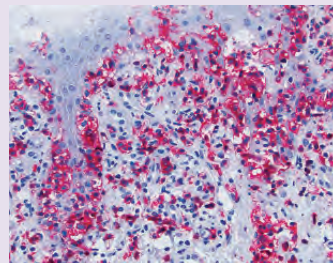
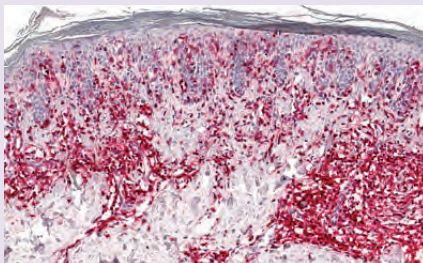
Acanthosis, papillomatosis, band-like infiltrate in the upper dermis (right)



Epidermotropic infiltrate



CD4+ (left).
Variant: CD8+ (right)



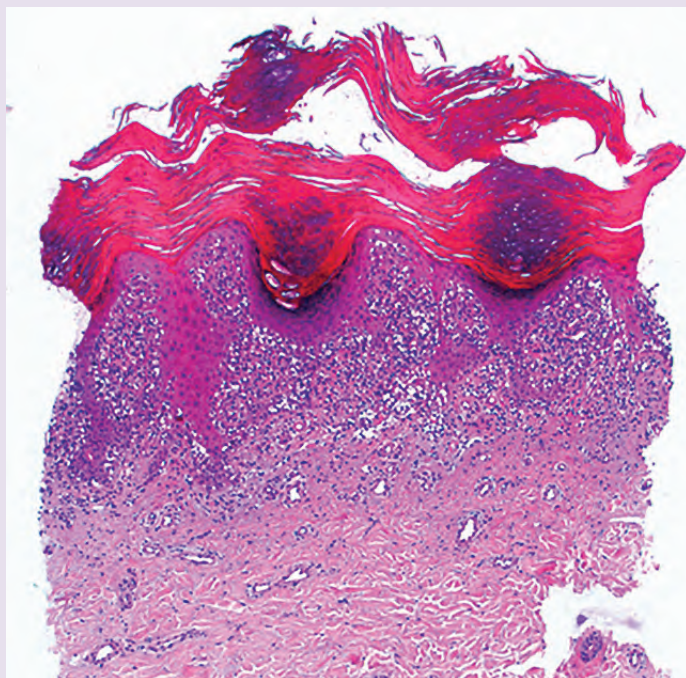
MYCOSIS FUNGOIDES

Mycosis Fungoides Plaque Stage II, Planta

Plantar
hyperkeratotic
plaque



Plantar
hyperkeratosis
and acanthosis.
Band-like
subepidermal
infiltrate



Cl: After some years or even decades, patches transform into infiltrated, sometimes itchy plaques.

Hi: In this stage of the disease, the diagnosis can be made due to typical histopathological features.

- Variable hyperkeratosis
- Acanthosis and papillomatosis of the epidermis with elongation of the rete ridges
- Edema in the papillary dermis
- Band-like infiltrate of small lymphocytes with cerebriform nuclei in the upper dermis

MYCOSIS FUNGOIDES

- Epidermotropism of lymphocytes:
 - Single cells in the basal layer, especially on the tips of rete ridges
 - Small intraepidermal clusters (Pautrier microabscesses)
 - Intraepidermal lymphocytes have a halo and appear larger than small lymphocytes in the dermis
- Eosinophils and plasma cells present
- Prominent postcapillary (high endothelial) venules in the upper and mid dermis. This is commonly seen in all cutaneous T-cell infiltrates and is not specific for cutaneous T-cell lymphomas

Variant: CD8+ Mycosis Fungoides

CI: Corresponds to the classic CD4+ type of mycosis fungoides. Good prognosis.

Hi:

- Superficial band-like infiltrate
- Epidermotropism of lymphocytes
- Absence of apoptotic keratinocytes. No necrosis
- Small lymphocytes. Subtle nuclear atypia
- Intraepidermal CD8+ T-cell clone, occasionally pagetoid infiltration into the epidermis as seen in pagetoid reticulosis (see below)

Immunophenotype: CD2–, CD3+, CD4–, CD5–, CD8+, TIA-1+, CD7+.

Reference

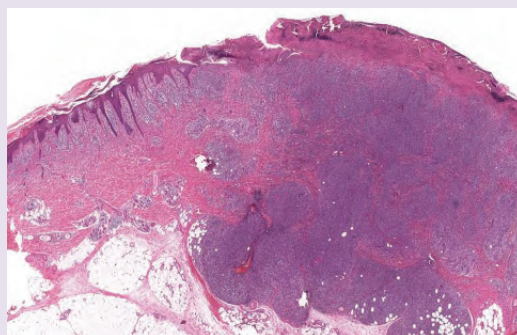
Nikolaou, V.A., Papadavid, E., Katsambas, A., et al. (2009) Clinical characteristics and course of CD8+ cytotoxic variant of mycosis fungoides: a case series of seven patients. *Br J Dermatol* **161**(4): 826–30.

Mycosis Fungoides Tumor Stage III

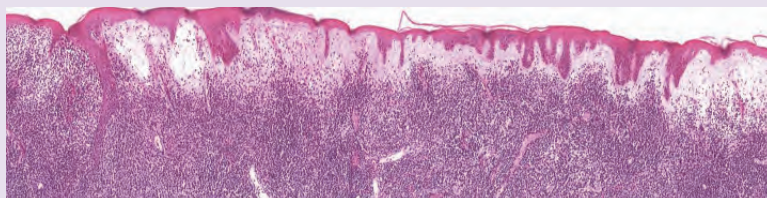
Tumorous lesions on the trunk (left)



Band-like infiltrate in the upper dermis and nodular in the mid and deep dermis (right)

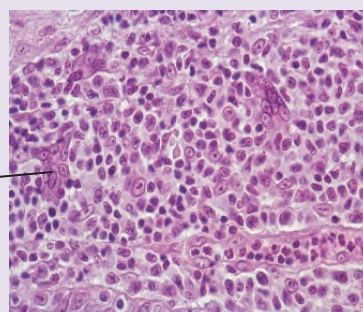
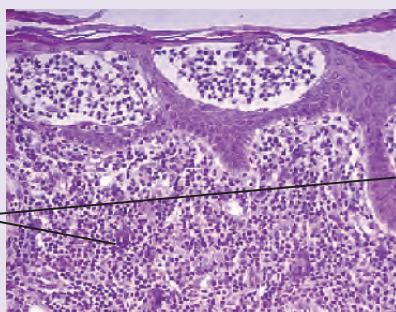


Subepidermal edema



Pautrier microabscesses

Postcapillary venules



MYCOSIS FUNGOIDES

Cl: Soft tumors, developing either on normal-looking skin (d'emblée) or on pre-existing plaques. Surface mostly ulcerated.

Hi:

- Nodular and diffuse infiltrate, covering all layers of the dermis
- Epidermotropism may be lost
- In addition to a predominant population of small cerebriform cells, there is a variable admixture of immunoblasts, lymphoblasts, and medium-sized or large pleomorphic or anaplastic cells
- When transformation into higher malignancy occurs, large atypical CD30+ cells appear and may even predominate

Immunohistochemistry: The typical phenotype of the neoplastic cell is CD2+, CD3+, CD5+, CD4+, CD45RO+, beta-F1+, CD8-. In rare cases expression of CD30 is found in the patch or plaque stage. In tumor stage, expression of CD30 by a variable number of large tumor cells is observed. In rare cases, expression of CD8 and TCRdelta can occur. As the disease progresses, an aberrant phenotype with loss of mature T-cell antigens is a common finding.

Reference

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Comment: Functionally, the neoplastic cells in MF express TH2 phenotype, which accounts for many systemic changes associated with MF due to the production of a TH2-specific cytokine pattern (IL-4, IL-5, IL-10, and others) leading to eosinophilia, increase of IgE or IgA, impaired delayed type reactivity, and itching.

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Molecular biology: TCR beta or gamma chain genes are clonally rearranged in most cases of mycosis fungoides.

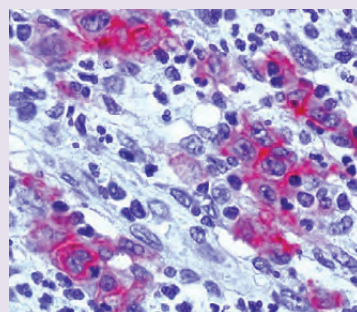
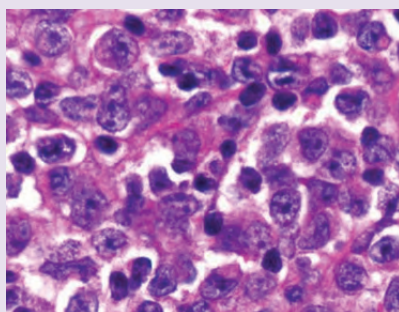
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Large Cell Transformation

Small and large atypical lymphoid cells (left)

CD30+ cells (right)



Cl: Plaques or tumors may show sudden progression, different from the indolent course in past years. Involvement of mucous membranes, which usually are unaffected in “classic” mycosis fungoides, may occur.

Hi:

- Loss of epidermotropism

- The hallmark is the appearance of large atypical cells with pleomorphic nuclei and abundant cytoplasm within the infiltrate of predominantly small cerebriform lymphocytes. These large cells express the CD30 antigen

SIMULATORS AND VARIANTS OF MYCOSIS FUNGOIDES

Simulators and Variants of Mycosis Fungoides: "Parapsoriasis"

The term *parapsoriasis* is confusing. It encompasses a number of different pathological states clinically manifested by chronic recalcitrant erythematous scaling lesions.

In the context of mycosis fungoides, three types have to be differentiated.

- "Parapsoriasis en gouttes" (guttate parapsoriasis; pityriasis lichenoides chronica; parapsoriasis guttata of Jadassohn and Juliusberg). Nosologically, it is completely unrelated to mycosis fungoides
- "Parapsoriasis lichenoides," featuring a poikilodermatous appearance
- "Parapsoriasis en plaques" (Brocq's disease), referred to as small plaque parapsoriasis

The common features of the subgroups described by Brocq are:

- Long duration of the disease
- Good general health
- Absence of itching
- Erythema and pityriasiform scaling
- Control of disease without cure by topical treatment
- Round cell infiltrate in the papillary dermis

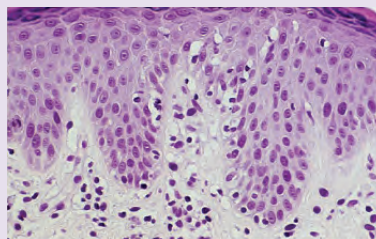
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Simulator: Small Plaque Parapsoriasis (SPP) (Brocq's Disease, Digitate Dermatitis)

Small macules along the tension lines on the trunk (left)

Scattered lymphocytes in the papillary dermis (right)



Cl: Round or oval well-circumscribed macules preferentially on the trunk along the tension lines of the skin. This disease shares some features with early patch-stage mycosis fungoides. However, the clinical, histological, and prognostic characteristics favor a nosological disease, whereas large plaque parapsoriasis (see below) is identical with early patch-stage mycosis fungoides.

Hi: Simulates normal skin.

- Epidermis normal or slightly acanthotic
- Some scattered lymphocytes in the dermis
- No marked epidermotropism, in contrast to early lesions in MF
- No edema in the papillary dermis

References

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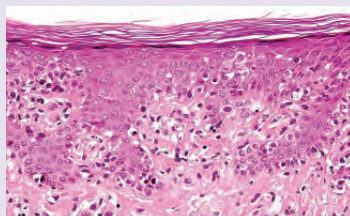
Schmoekel, C., Burg, G., and Braun, F.O. (1979) Quantitative analysis of lymphoid cells in mycosis fungoides, Sezary's syndrome and parapsoriasis en plaques. *Arch Dermatol Res* **264**(1): 17–28.

SIMULATORS AND VARIANTS OF MYCOSIS FUNGOIDES

Large Plaque Parapsoriasis (LPP)

Large plaques
on the trunk
(left)

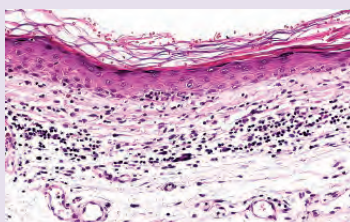
Epidermotropic
infiltrate (right)



Variant: Large Plaque Parapsoriasis with Poikiloderma

Poikiloderma
(left)

Atrophy of the
epidermis (right)



Large plaque parapsoriasis is an indolent form of early patch-stage mycosis fungoides, showing no or only slow progression over years or decades. This distinct favorable prognosis has an impact on therapy, which should be conservative and topical rather than aggressive and systemic.

CI: Preferentially on the trunk there are large (>10 cm), fairly demarcated, irregularly shaped erythematous patches with pityriasisform scaling. *Poikiloderma atrophicans vasculare* is a special variant occurring in light protected areas and showing a reticular network of hyperpigmentation, atrophy, and telangiectasia. Transformation into the plaque and tumor stages of mycosis fungoides may occur after decades.

Hi:

- Epidermis is normal or slightly acanthotic. The poikilodermatous variant shows atrophy of the epidermis
- Scarce lymphocytic infiltrate in the papillary dermis
- Single cell epidermotropism with arrangement of lymphocytes along the basal layer
- Spongiosis usually is absent
- Intraepidermal lymphocytes are often larger than those seen in the dermal infiltrate

Immunophenotype and Genetic Features: CD4+, CD8–, CD45RO+, beta-F1 +.

Genotype: Clonal T-cell receptor rearrangement in about 50% of cases.

Reference

Burg, G., Kempf, W., Dummer, R., and Kazakov, D.V. (2005) Large plaque parapsoriasis with and without poikiloderma. In: Burg, G. and Kempf, W. (eds) *Cutaneous Lymphomas*. Boca Raton: CRC Press.

Pigmented Purpuric Mycosis Fungoides

CI: Hyperpigmented, mostly macular lesions.

Hi: Erythrocyte extravasation. Hemosiderin in macrophages of the upper dermis.

DD: Lichenoid pigmented purpuric dermatitis of Gougerot–Blum.

Reference

Lor, P., Krueger, U., Kempf, W., Burg, G., and Nestle, F.O. (2002) Monoclonal rearrangement of the T cell receptor gamma-chain in lichenoid pigmented purpuric dermatitis of gougerot-blum responding to topical corticosteroid therapy. *Dermatology* **205**(2): 191–3.

Erythrodermic Mycosis Fungoides

CI: In primary erythroderma, as seen in Sézary syndrome (see below), 100% of the skin is involved from the beginning of the disease. Due to local tissue pressure (skin folds), clinically some areas may seem to be uninvolved (“deck-chair sign”). Erythroderma in mycosis fungoides

SIMULATORS AND VARIANTS OF MYCOSIS FUNGOIDES

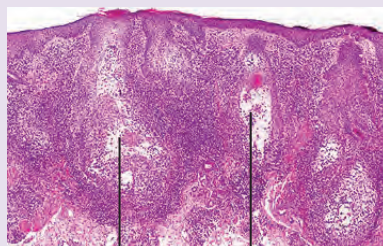
may result from secondary confluence of patches and plaques, leaving non-erythematous islands of uninvolved skin in between, showing at least 80% of skin surface involved. Besides

erythema, there usually is pityriasiform scaling and itching.

Hi: Corresponds to the patch or plaque stage of the disease.

Folliculotropic (Pilotropic) Mycosis Fungoides

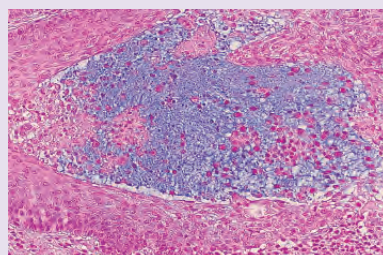
Flat ulcerated nodule on the capillitium



Follicular mucinosis

DD of Folliculotropic MF: Idiopathic Mucinosis Follicularis

Circumscribed flat plaque in the face



Mucin deposits

Cl: Folliculotropic MF and MF-associated follicular mucinosis belong to a spectrum of MF with a predilection for hair follicles. It presents as erythematous patches or plaques with follicular hyperkeratosis producing comedo-like plugs and often hair loss. Two prognostic subgroups are distinguished: early and advanced disease. The prognosis of the advanced form is worse than in non-follicular variants of MF.

Hi:

- Variably dense lymphocytic infiltrates surrounding and infiltrating the hair follicles and sparing more or less interfollicular skin
- Small to medium-sized lymphocytes with irregular nuclei
- Exocytosis of lymphocytes into the follicular epithelium
- Cystic dilation of the follicles, cornified plugging
- Mucin deposition in the hair follicle epithelia in 50–70% of cases

DD: Idiopathic mucinosis follicularis (Pinkus) showing mucin deposits in the hair follicles without association with cutaneous lymphoma; other forms of mycosis fungoides.

References

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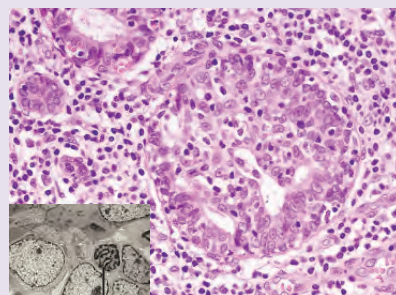
SIMULATORS AND VARIANTS OF MYCOSIS FUNGOIDES

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Syringotropic Mycosis Fungoides (Syringolymphoid Hyperplasia with Alopecia)

Hairless plaque on the trunk (left)

Lymphocytes in and around hyperplastic glandular structure (right)



Electron microscopy: cerebriform lymphocyte between glandular epithelial cells

Cl: Male preponderance. Red-brown slightly infiltrated scaling flat plaque. Anhidrosis and hair loss in the affected areas are common.

Hi:

- Proliferation of small eccrine epithelial islands
- Small cerebriform lymphocytes invading both the secretory and ductal portions of hyperplastic eccrine glands
- Epidermotropism is not a prominent feature
- Destruction of hair follicles by the neoplastic infiltrate
- Mucinous degeneration is typically lacking

Immunohistochemistry: CD3+, CD4+, CD8–.

DD: Idiopathic syringolymphoid hyperplasia.

References

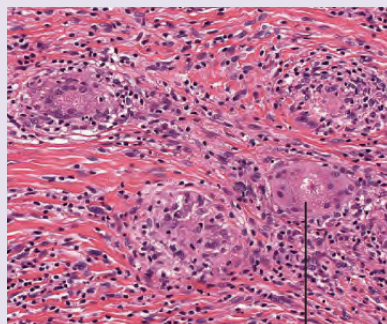
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GRANULOMATOUS SLACK SKIN

Granulomatous Mycosis Fungoides

Hyperpigmented crusted patches and plaques on the leg (left)

Fibrosis and focal granulomas with multinucleated giant cells (right)



Asteroid body

Granulomatous changes are frequently seen in cutaneous T-cell lymphomas. The granulomatous process may represent a local tissue response to the infiltrating malignant cells. The influence of granulomatous features on the prognosis is debated but most studies indicate an impaired prognosis.

Cl: Hyperpigmented patches and plaques.

Hi:

- Granulomatous infiltrates, composed of histiocytes, macrophages, and multinucleated giant cells, sometimes hiding the underlying mycosis fungoides
- Small lymphocytes with only subtle nuclear atypia
- Epidermotropism is lacking in 50% of cases

Immunophenotype: CD 3+, CD4+, CD8+/-.

Genotype: Clonal T-cell receptor rearrangement.

DD: Cutaneous sarcoidosis; deep fungal infection.

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Granulomatous Slack Skin

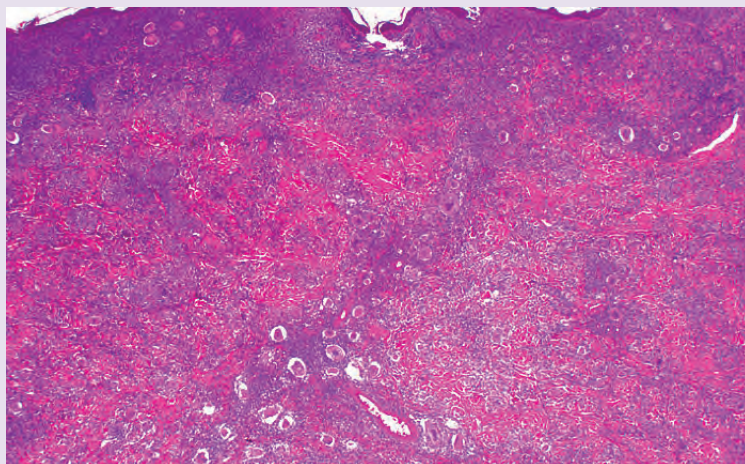
“Slack” skin in the axillary fold (left) and on the hip of the (lying) patient (right)



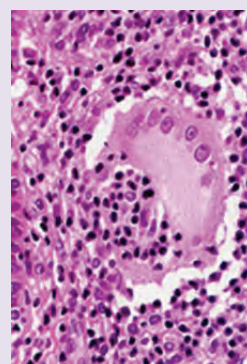
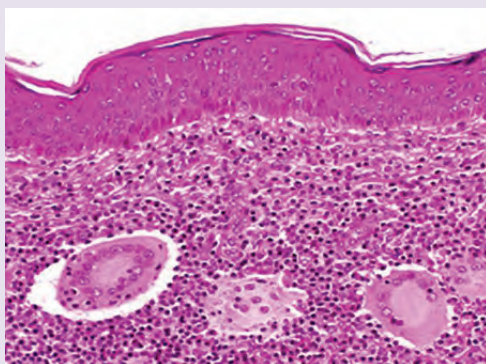
GRANULOMATOUS SLACK SKIN

Granulomatous Slack Skin

Multinucleated giant cells in a background of lymphoid infiltrate



Multinucleated giant cells with phagocytosed lymphocytes (emperipolesis)



Emperipolesis

Cl: Intertriginous areas, especially the axillary and inguinal areas show “slack” skinfolds due to bulky lymphoid infiltrates and loss of elastic fibers. In non-intertriginous areas, the folding of the slack skin is less obvious and presents as lax skin, resembling cutis laxa.

Hi:

- Loosely distributed, single-layer multinucleated histiocytic giant cells, containing 20–30 nuclei located at the periphery of the abundant eosinophilic cytoplasm within a dense infiltrate of small lymphocytes
- Giant cells contain remnants of elastic fibers and engulfed lymphoid cells. This phenomenon is referred to as *emperipolesis*
- Background of mycosis fungoides showing small cerebriform lymphocytes with variable epidermotropism

- Loss of elastic fibers at the sites of the infiltrate
- DD:** Cutis laxa.

References

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PAGETOID RETICULOSIS

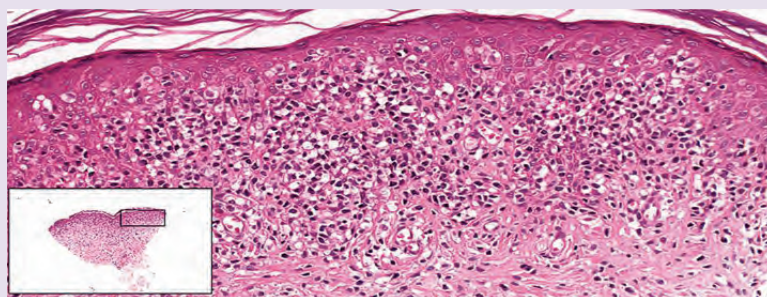
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Pagetoid Reticulosis (PR), Unilesional (Woringer-Kolopp)

Well demarcated psoriasiform lesion



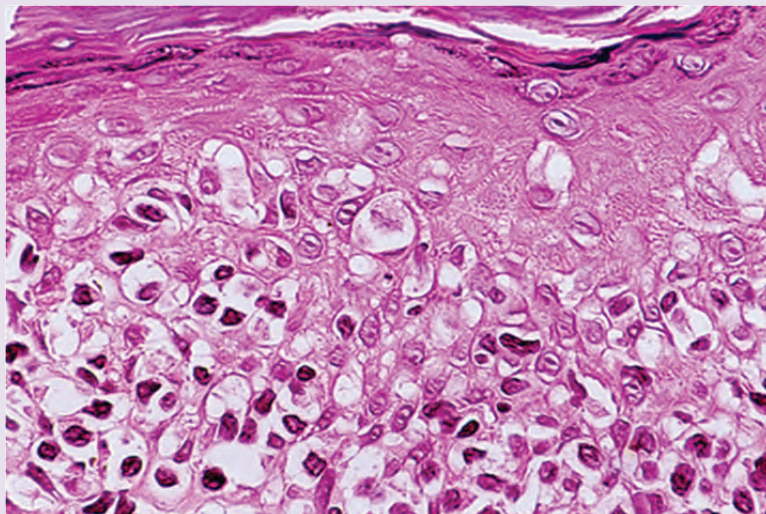
Epidermotropic band-like infiltrate in the epidermis and the upper dermis



SÉZARY SYNDROME (SS)

Pagetoid Reticulosis (PR), Unilesional (Woringer–Kolopp)

Sponge-like disaggregation of keratinocytes by lymphoid cells with abundant cytoplasm



The term *pagetoid reticulosis*, proposed by Braun-Falco, should be used to designate only the unilesional Woringer–Kolopp type. The term *disseminated Ketrone and Goodman type* is no longer used since it represents other forms of CTCL.

Cl: Solitary psoriasiform or bowenoid erythematous, scaling or crusty centrifugally growing plaque with preferential acral localisation.

Hi:

- Marked psoriasiform hyperplasia of the epidermis with para- and orthohyperkeratosis

- Sponge-like disaggregation of the acanthotic epidermis by medium-sized to large atypical lymphoid cells with vacuolated, abundant cytoplasm, singly or arranged in clusters
- Single cells and small clusters of tumor cells can also be observed within the epithelia of adnexal structures

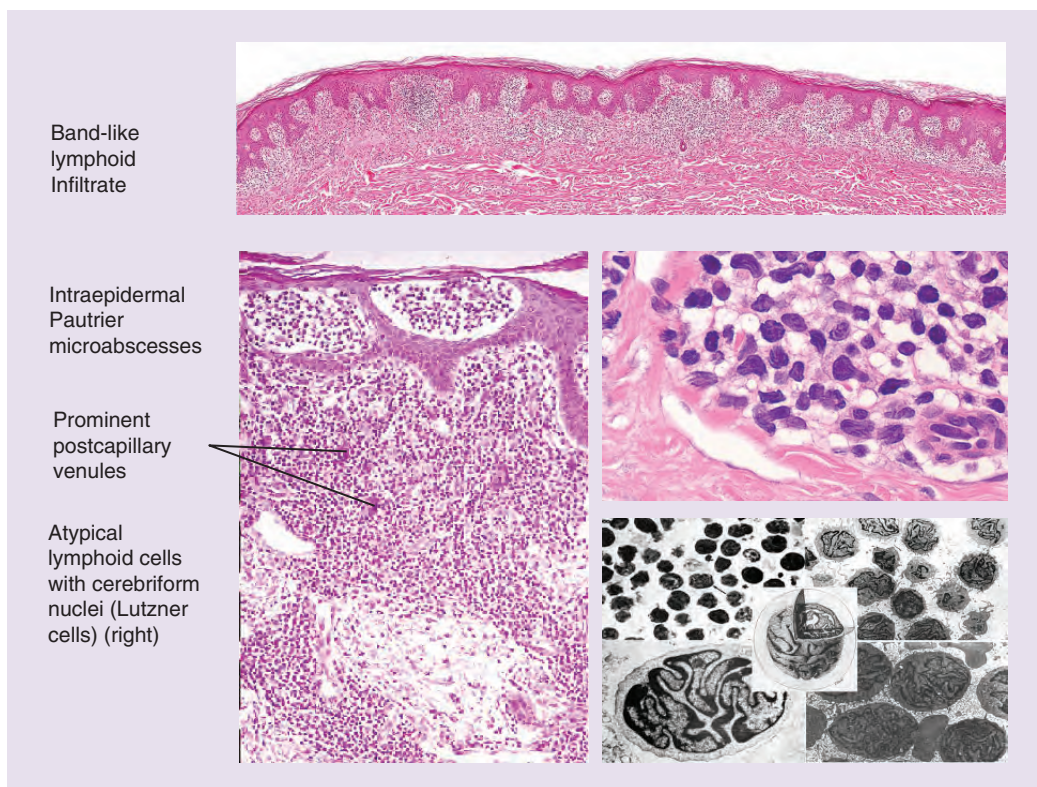
Sézary Syndrome (SS)

Erythroderma, swelling of lymph nodes, scaling (left)

“Nappes claires” (right top) and palmar hyperkeratosis (right bottom)



SÉZARY SYNDROME (SS)



Cl: (Primary) edematous erythroderma with scaling and “nappes claires” (“deck-chair sign”; non-erythematous skinfolds), generalized lymphadenopathy, intense pruritus, palmoplantar hyperkeratosis, diffuse alopecia, onychodystrophy, leukemic spread of tumor cells with atypical cerebriform nuclei (Lutzner cells).

Hi:

- Psoriasiform acanthosis of the epidermis
- Lichenoid subepidermal perivascular or band-like infiltrate composed of predominantly small lymphocytes with or without nuclear atypia
- Epidermotropism and lining up of lymphocytes with cerebriform nuclei
- Pautrier microabscesses not regularly present
- Edema in the upper dermis, followed by fibrosis

Lymph nodes show dermatopathic changes in early stages of the disease, whereas effacement of normal architecture by a dense, diffuse, and monotonous infiltration of small lymphoid cells is found in later stages with specific involvement.

Immunophenotype : CD 2+, CD 3+, CD4+, CD 5+, CD 45RO+, CD 30-. Expression of PD-1 and TOX by more than 50% of the lymphocytes.

Genotype: Clonal T-cell receptor rearrangement.

DD: The so-called red man syndrome encompasses cases of erythroderma which cannot be assigned to any other underlying disease such as atopic dermatitis, psoriasis, and pityriasis rubra pilaris.

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SÉZARY SYNDROME (SS)

Thestrup-Petersen, K., Halkier-Sorensen, L., Sogaard, H., and Zachariae, H. (1988) The red man syndrome. Exfoliative dermatitis of unknown etiology: a description and follow up of 38 patients. *J Am Acad Dermatol* **18**: 1307–12.

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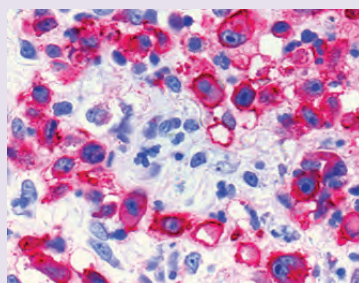
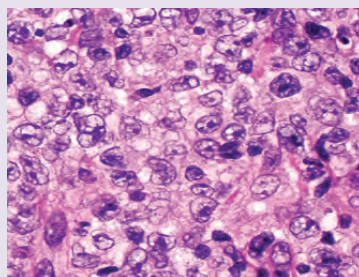
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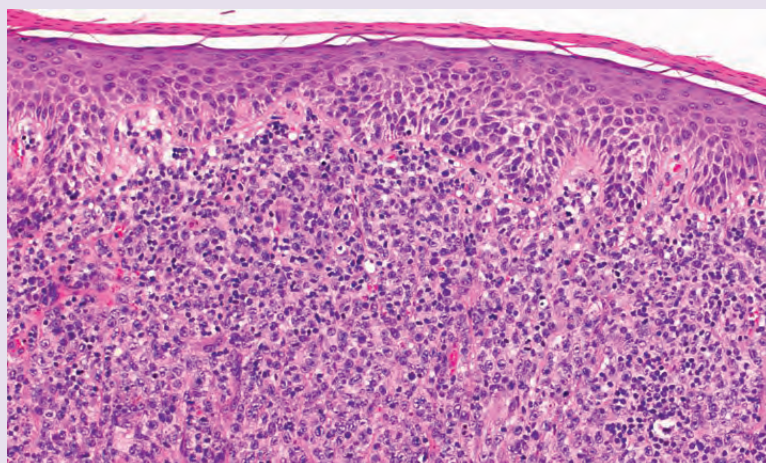
Variant: Sézary Syndrome, Large Cell Transformation

Tumorous lesion on the neck in Sézary syndrome (left)

Large pleomorphic cells (right top), CD30+ (right bottom)



Dense infiltrate of pleomorphic lymphoid cells in the dermis. No or little epidermotropism



CI: Development of nodules and tumors against the background of erythroderma.

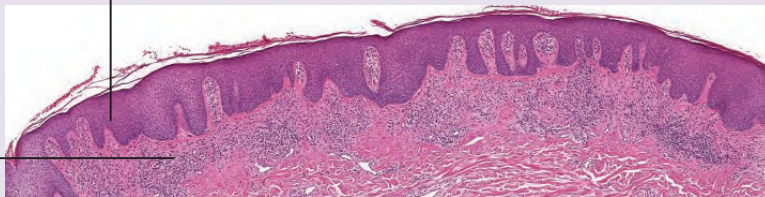
SÉZARY SYNDROME (SS)**DD of SS: Erythrodermic Atopic Dermatitis**

White
dermographism
in a patient with
atopic
erythroderma



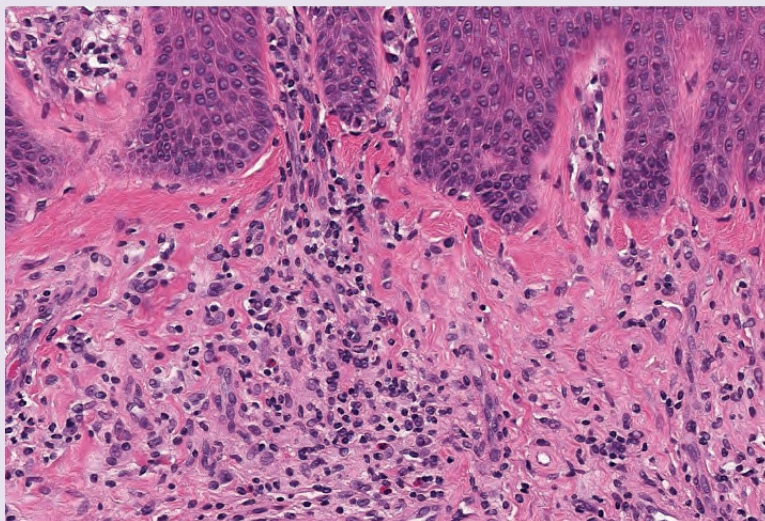
Broad acanthosis and
papillomatosis

Predominantly
lymphocytic
inflammatory
infiltrate in the
upper dermis,
without epider-
motropism
or edema



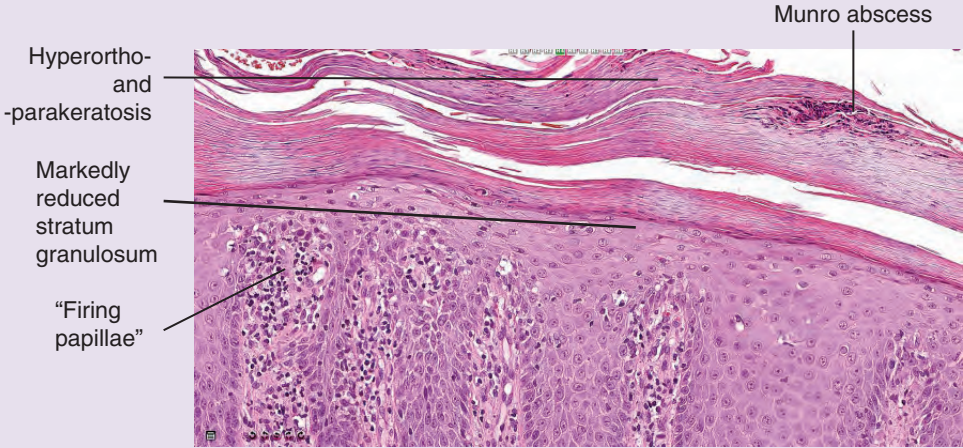
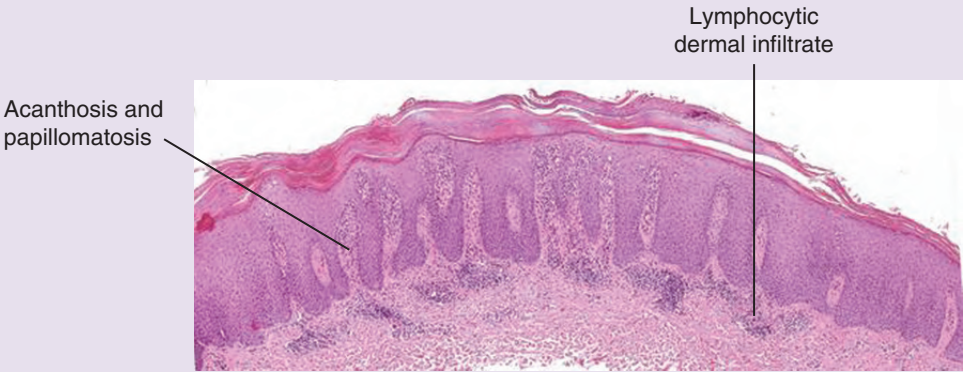
Predominantly
lymphocytic
inflammatory
infiltrate

Scattered
eosinophils



SÉZARY SYNDROME (SS)

DD of SS: Erythrodermic Psoriasis



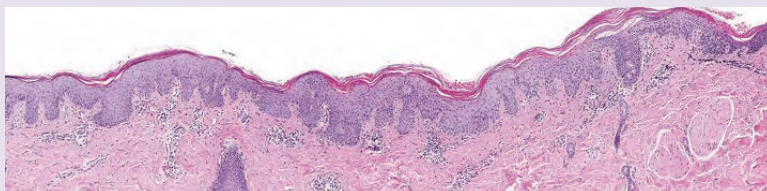
SÉZARY SYNDROME (SS)

DD of SS: Pityriasis Rubra Pilaris

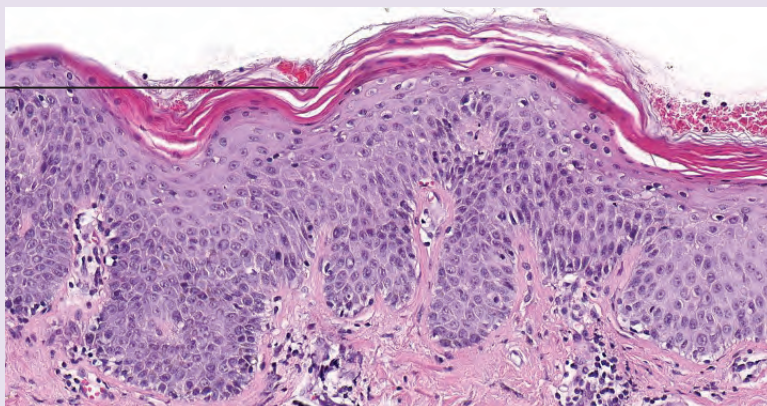
Erythematous patches and follicle-bound infiltrates



Plump acanthosis and papillomatosis (mid and bottom)



Horizontally and vertically alternating ortho- and parahyperkeratosis



Sparse inflammatory infiltrate in the upper dermis

Hi:

- Large pleomorphic cells, sometimes CD30+
- Epidermotropism may be lost

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CD30-Positive Lymphoproliferative Disorders (LPD) of the Skin

CD30-positive T-cell lymphoproliferative disorders of the skin (CD30+ LPD) comprise a clinical and morphological spectrum of diseases including

CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

lymphomatoid papulosis (LyP), primary cutaneous CD30+ large T-cell lymphoma (CD30+ LTCL) as well as so-called borderline cases. The hallmark of the tumor cells is the expression of CD30, a cytokine receptor belonging to the tumor necrosis factor receptor (TNFR) superfamily.

References

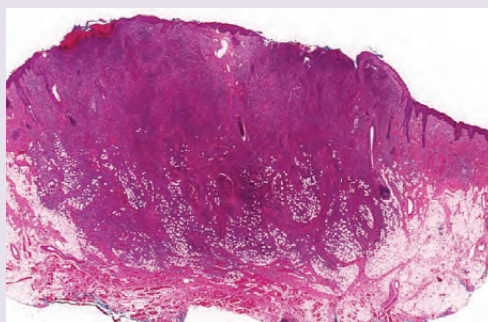
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Anaplastic Large Cell Lymphoma (ALCL)

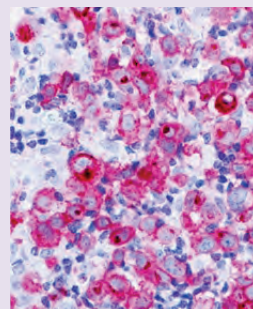
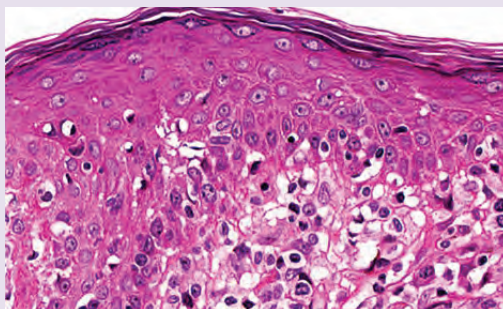
Multiple ulcerated nodules on the lower leg



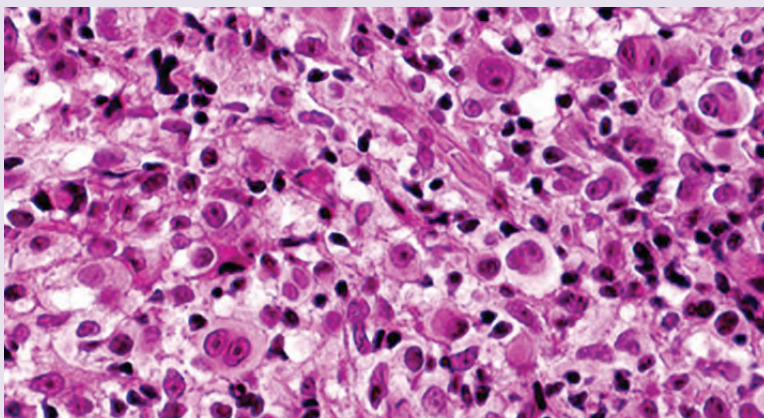
Dense infiltrate in the dermis and subcutis (right)



Epidermotropic cells (left). CD30+ (right)



Large anaplastic tumor cells



CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

Cl: Asymptomatic, mostly solitary, in 20% of cases multiple, firm, and often ulcerated nodules, which grow rapidly and are preferentially located on the extremities or the head. Most patients have a favorable prognosis.

Hi:

- Diffuse dense nodular infiltrate composed of cohesive sheets of atypical large lymphoid cells
- All levels of the dermis and also the subcutis are involved
- Epidermotropism usually is lacking
- The morphologic hallmark are large, pleomorphic (anaplastic) cells:
 - Irregularly shaped nuclei
 - Sometimes multinucleated
 - One or multiple nucleoli
 - Abundant, clear or eosinophilic cytoplasm
- Many mitoses
- Clusters of small reactive lymphocytes within and around the tumor
- Eosinophils, plasma cells, and accessory dendritic cells usually are not prominent

Immunohistochemistry: CD30+, CD2+, CD3+, CD4+, and CD45RO+, and activation markers such as CD25 (IL-2R), CD71, and HLA-DR. Translocation t(2;5)(p23;q35) and expression of anaplastic lymphoma kinase (ALK), usually found in nodal ALCL, are not found in primary cutaneous CD30+ LPD.

DD: Undifferentiated epithelial, mesenchymal, and melanocytic tumors with anaplastic morphology.

References

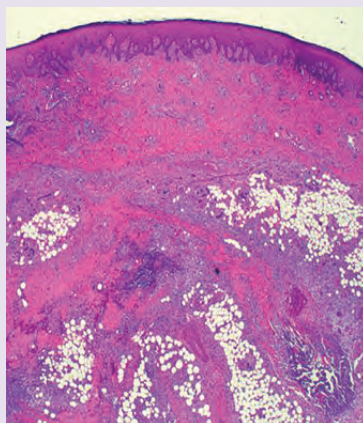
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CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

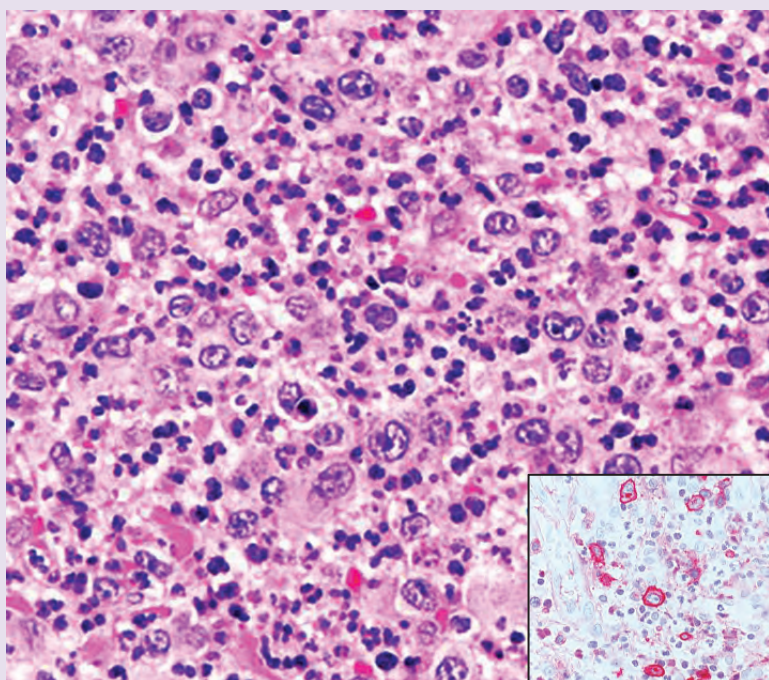
Neutrophil-Rich (Pyogenic) Anaplastic Large Cell Lymphoma

Flat ulcerated tumor

Inflammatory infiltrate in the dermis and subcutis (right)



Neutrophil rich inflammatory infiltrate with a few large CD30 positive tumor cells (inset)



CI: Nodular tumor(s) preferentially in the face, ulcerated and abscess-forming, simulating pyoderma gangrenosum or deep vegetating fungus infection. Soft nodules may also appear on the trunk and extremities. High amounts of IL-8 produced by a few CD30+ tumor cells are responsible for the neutrophil-rich inflammatory infiltrate.

Hi:

- Abscess-like inflammatory infiltrate, predominantly composed of neutrophils
- Loosely distributed, large atypical cells, CD30+

DD: Pyoderma gangrenosum; abscess; deep fungal infection.

CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

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Lymphomatoid Papulosis

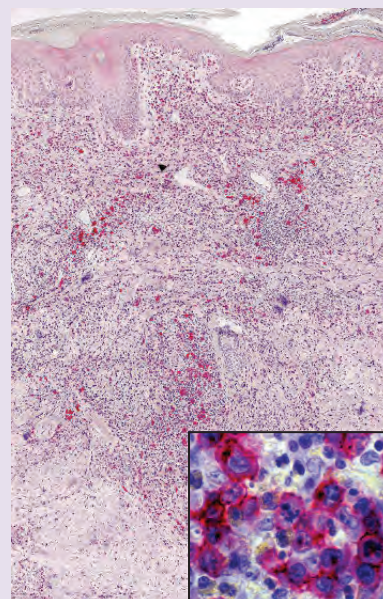
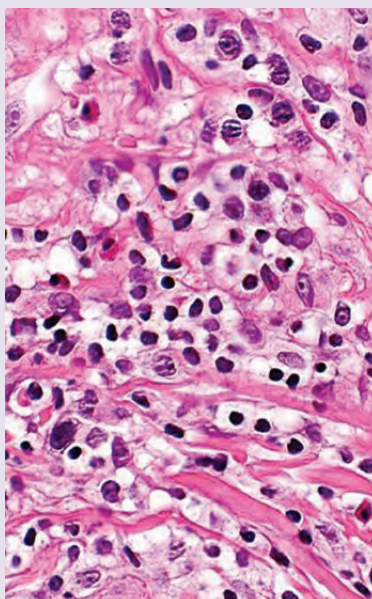
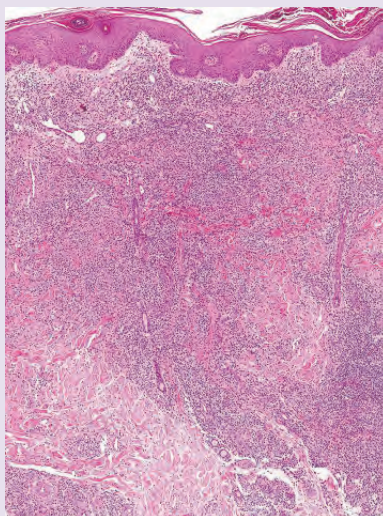
Papules in various stages of development (left)

Early (bottom left) and healed lesion with scar formation (bottom right)

Dense wedge-shaped infiltrate in the dermis (right)

Mixed cellular infiltrate consisting of lymphocytes, eosinophils and scattered large atypical cells (left)

Scattered CD30+ cells in LYP type A (right and inset)



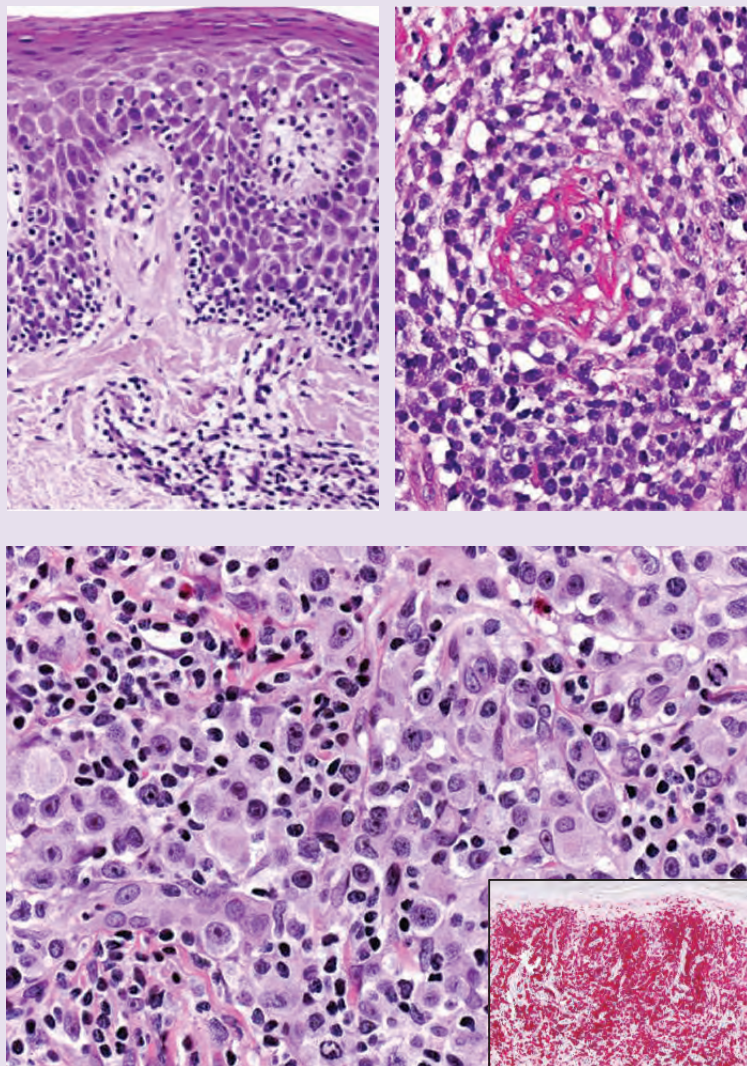
CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

Lymphomatoid Papulosis

Epidermotropic LYP type B (left)

Angioinvasive angiocentric LYP type E (right)

Cohesive sheets of large atypical cells in LYP (mixture of type A and C); CD30 positive (inset)



In 1968, Macaulay described a chronic recurrent, self-healing, papulonodular skin eruption with histological features of a high-grade lymphoma.

Cl: Disseminated papules and/or small nodules, which within days or a few weeks become red-brown, hemorrhagic or pustular and finally undergo ulceration, followed by complete spontaneous regression of the lesion, occasionally leaving behind hyper- or hypopigmented varioliform scars.

Hi: Broad spectrum with variably dense infiltrates of medium-sized to large atypical pleomorphic CD30+ cells are the hallmarks of the disease. Depending on the lesion's stage of evolution, the

histological presentation is different. In fresh lesions, there is a wedge-shaped infiltrate of tumor cells with ulceration.

Various subtypes have been differentiated.

- Type A: scattered CD30+ cells
- Type B: epidermotropic, small CD30–/+ cells
- Type C: cohesive large CD30+ cells
- Type D: epidermotropic, small CD30+, CD8+ cells
- Type E: angioinvasive, medium/large CD30+, CD8+ cells
- Type 6p25.3 rearrangement (*DUSP22-IRF4* fusion gene)

Immunophenotype: CD3+, CD4+/-, CD8-/+ , CD25+, CD30+, TIA-1+, granzyme B+, CD56-/+ [10%].

Genotype: Clonal T-cell receptor rearrangement in 50% of cases.

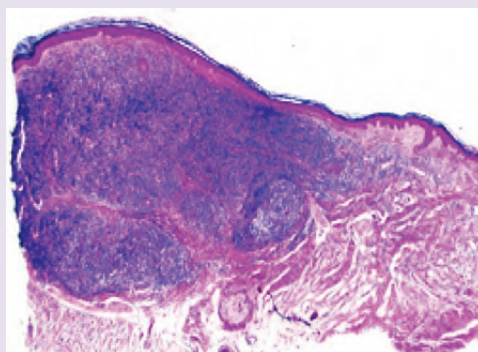
DD: Anaplastic large cell lymphoma.

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Differential Diagnosis: Hodgkin's Lymphoma, Lymphocyte Predominance

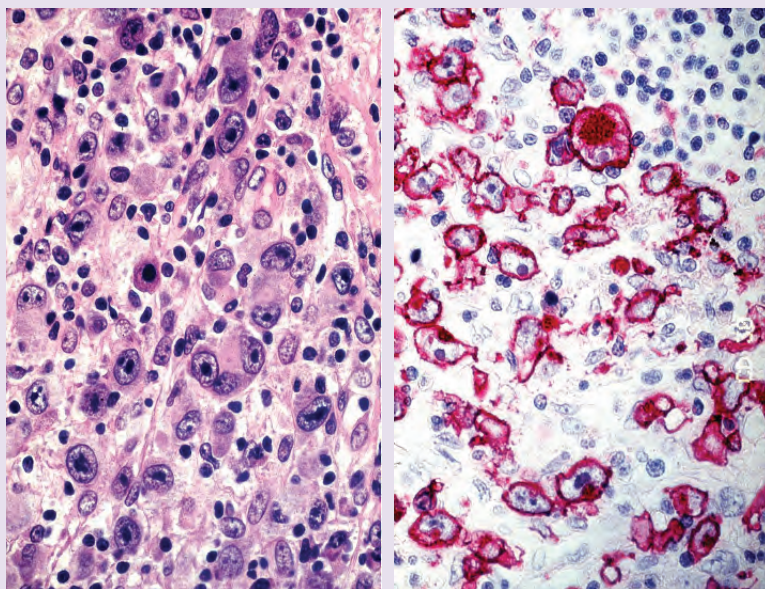
Nodules on the arm (left) and nodular infiltrate in the dermis (right) in "primary" cutaneous HD



CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS (LPD)

Differential Diagnosis: Hodgkin's Lymphoma, Lymphocyte Predominance

Hodgkin cells
and Sternberg-
Reed cells (left),
CD30+ (right)



CI: There have been reports on primary cutaneous Hodgkin's disease, but its existence is very questionable, and most probably these lesions are CD30+ anaplastic large cell lymphomas. However, they may represent retrograde lymphatic spread of Hodgkin's disease from affected lymph nodes or result from extension per continuitatem.

Hi: Mixed cellularity: Reed–Sternberg cells, Hodgkin cells, eosinophils, neutrophils, small lymphocytes. T- or B-cell phenotype.

Immunophenotype: Reed–Sternberg cells express CD15, CD30, and MUM-1.

DD: Anaplastic large cell lymphoma; lymphomatoid papulosis.

References

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SUBCUTANEOUS PANNICULITIS-LIKE LYMPHOMA

Subcutaneous Panniculitis-Like Lymphoma

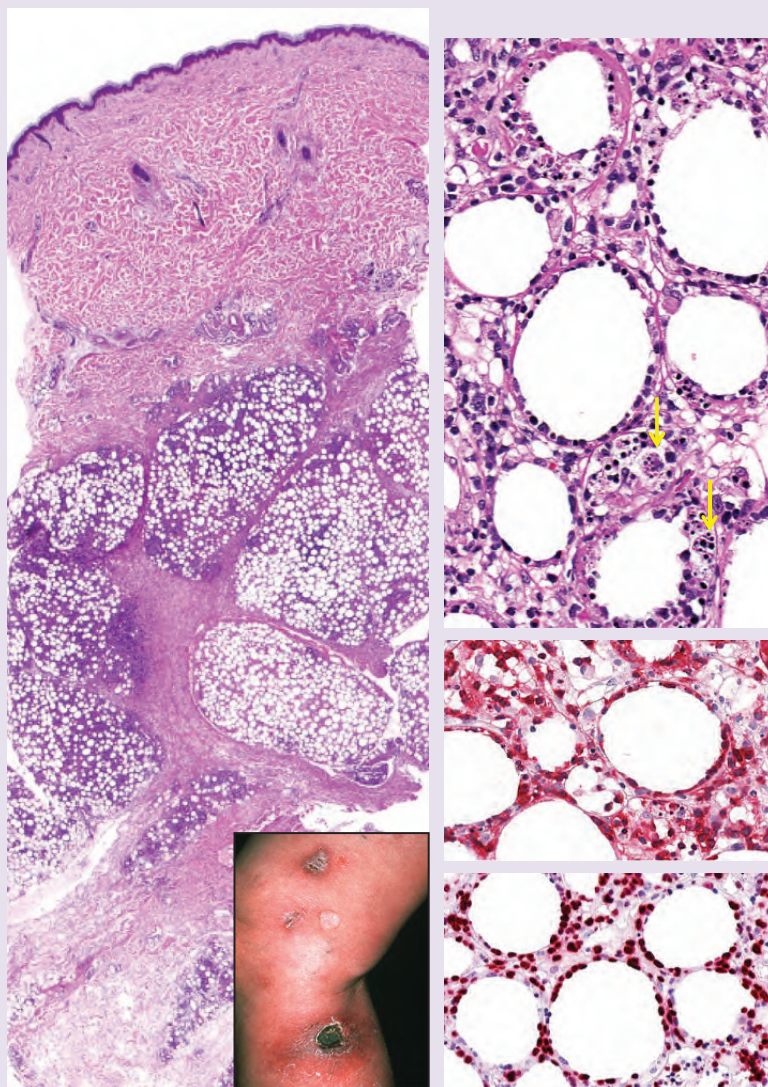
Subcutaneous (Panniculitis-Like; Alpha/Beta) T-Cell Lymphoma

Predominantly lobular infiltrate in the subcutis with septal fibrosis (left)

Inset: panniculitis-like lesions on the leg with necrosis

Lymphoid infiltrate rimming around fat vacuoles (upper right); hemophagocytosis (arrows)

CD8 (mid right) and Ki67/MIB-1 (bottom right) positive tumor cells



Cl: Subcutaneous nodules, simulating panniculitis; usually no ulceration.

Hi:

- Subcutaneous lobular infiltrates
- Small, medium-sized to large pleomorphic lymphocytes
- Lymphocyte-rimming of adipocytes (not specific!)
- Karyorrhexis and phagocytosis of nuclear debris

Immunophenotype: CD3+, CD4-, CD8+, CD56-, TIA-1+, granzyme B+, perforin+, EBER-, LMP-1-, beta-F1+ (TCR alpha/beta). Demonstration of expression of TCR alpha/beta is essential as it is the defining criterion for this lymphoma.

Genotype: Clonal rearrangement of alpha/beta T-cell receptor.

DD: Panniculitis; subcutaneous gamma/delta lymphoma.

SUBCUTANEOUS PANNICULITIS-LIKE LYMPHOMA

References

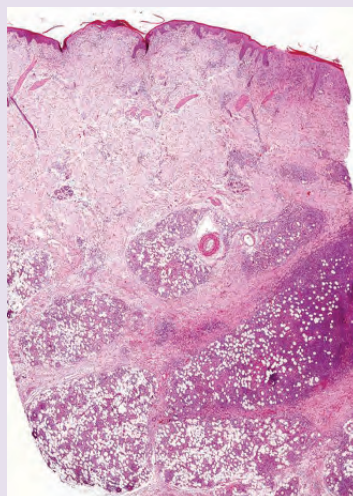
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Differential Diagnosis: Subcutaneous (Panniculitis-Like) Gamma/Delta Lymphoma

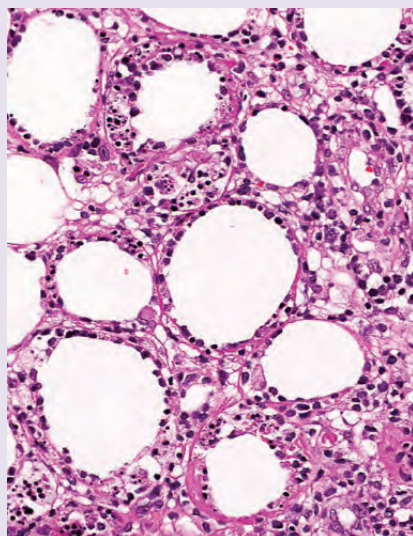
Panniculitis-like lesions on the leg (left)



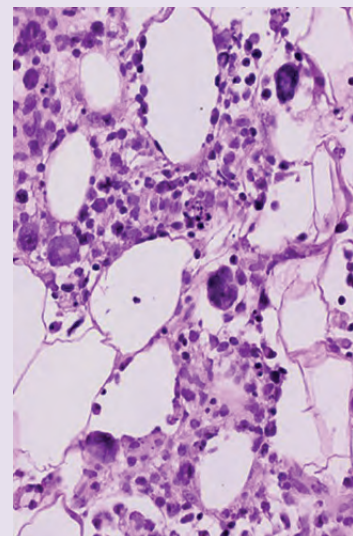
Panniculitis-like septal and lobular infiltrate in the subcutaneous tissue (left)



Rimming of tumor cells around fat vacuoles (left)



Scattered large atypical cells (right)



SUBCUTANEOUS PANNICULITIS-LIKE LYMPHOMA

Cl: Subcutaneous nodular infiltrate. Usually aggressive, rapidly progressive course. However, less aggressive variants producing high levels of interferon gamma have been reported.

Hi:

- Lobular panniculitis-like infiltrate in the subcutis. In addition, dermal and epidermotropic infiltrates can be present
- Small and medium-sized lymphocytes with chromatin-dense atypical nuclei
- Rimming around fat cells
- Scattered large atypical lymphoblasts
- Karyorrhexis and phagocytosis of nuclear debris

Immunophenotype: CD3+, CD4-, CD8-, CD56+, TIA-1+, granzyme B+, beta-F1-, TCR gamma (or delta) +.

Genotype: Clonal rearrangement of the T-cell receptor.

DD: Panniculitis; subcutaneous panniculitis-like alpha/beta T-cell lymphoma.

References

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Differential Diagnosis: Lupus Panniculitis (Lupus Profundus)

Erythematous hyperkeratotic plaque

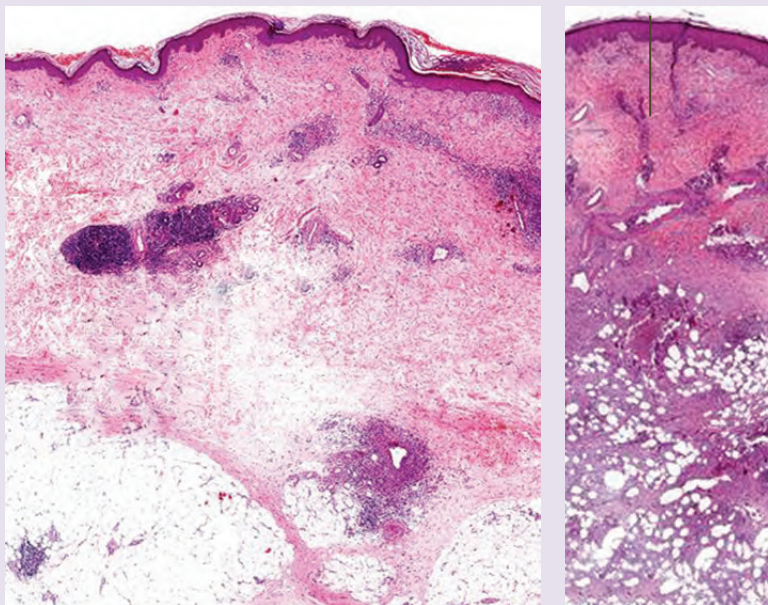


SUBCUTANEOUS PANNICULITIS-LIKE LYMPHOMA

Differential Diagnosis: Lupus Panniculitis (Lupus Profundus)

Nodular dense lymphocytic infiltrates (left)

Septal and lobular panniculitis (left and right)



Cl: Slightly elevated subcutaneous nodular lesion or plaque. The overlying epidermis is normal or retracted and sometimes may show involvement with erythema and firm hyperkeratosis. Ulceration may occur. Association with systemic or cutaneous lupus erythematosus possible.

Hi: Infiltrates in the deep dermis and in septa and lobules of the subcutaneous fat tissue. Mucin and admixture of plasma cells. Clusters of CD123-positive plasmacytoid dendritic cells.

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Primary Cutaneous Peripheral Lymphoma (PTL), Unspecified (NOS)

A heterogeneous group of cutaneous T-cell lymphomas that do not fit into one of the well-defined subtypes of T-cell lymphoma/leukaemia. It includes the following entities: (1) cutaneous gamma-delta T-cell lymphoma; (2) primary cutaneous small-medium CD4+ T-cell lymphoproliferative disorder (provisional); (3) primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (provisional).

PRIMARY CUTANEOUS PERIPHERAL LYMPHOMA (PTL), UNSPECIFIED (NOS)**Reference**

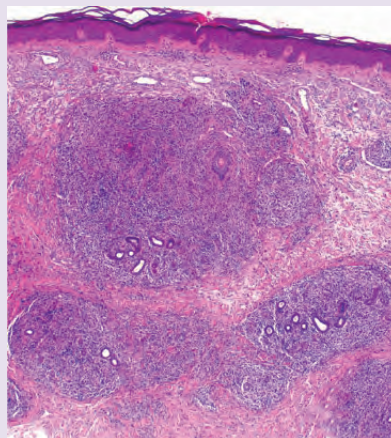
Ralfkiaer, E., Willemze, R., Meijer, C.J.L.M., et al. (2006) Primary cutaneous peripheral T-cell lymphoma, unspecified. In: LeBoit, P.E., Burg, G., Weedon, D.,

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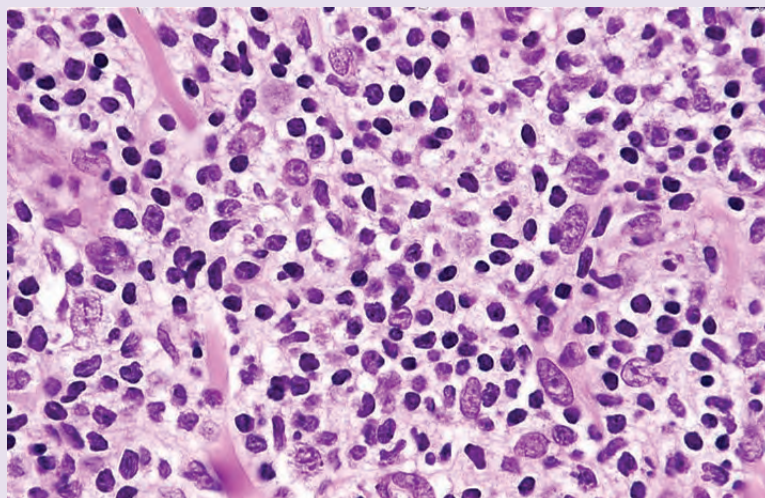
Primary Cutaneous CD4-positive (Acral) Small/Medium-Sized T-Cell Lymphoproliferative Disorder

Papules on the hand (left)

Nodular dermal infiltrate (right)



Small to medium-sized pleomorphic lymphoid cells



Cl: Circumscribed nodular lesion predominantly on the head and neck region, showing an indolent course with excellent prognosis.

Hi:

- Nodular dermal infiltrates
- No epidermotropism
- Small to medium-sized pleomorphic lymphoid cells

- Eosinophils
- Sometimes clusters of plasma cells

Immunophenotype: CD3+, CD4+, CD8-, CD30-, beta-F1+, PD-1+ (20–30% of the infiltrate).

Genotype: Monoclonal rearrangement of T-cell receptor in approximately 60% of cases.

DD: T-cell pseudolymphoma; primary cutaneous peripheral lymphoma (PTL), unspecified (NOS).

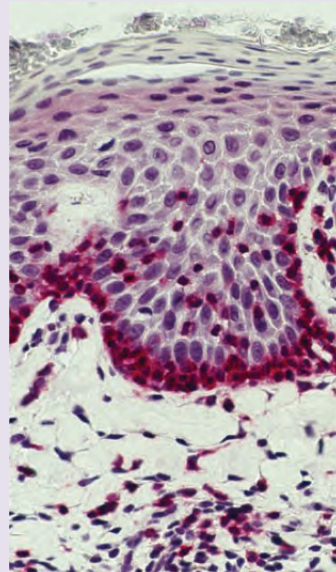
PRIMARY CUTANEOUS PERIPHERAL LYMPHOMA (PTL), UNSPECIFIED (NOS)

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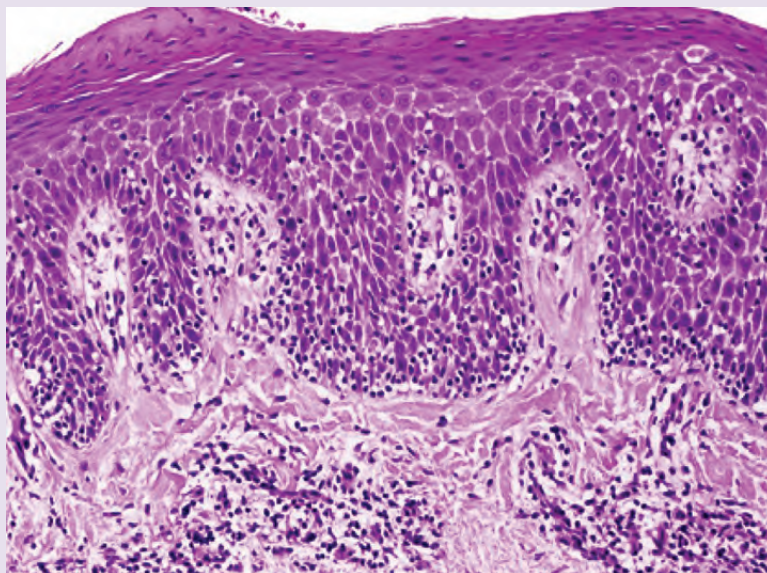
Cutaneous Aggressive Epidermotropic CD8-positive T-Cell Lymphoma (Berti)

Plaques in the groin (left). CD8+ cells in the epidermis (right)



CD8

Epidermotropic infiltrate



PRIMARY CUTANEOUS PERIPHERAL LYMPHOMA (PTL), UNSPECIFIED (NOS)

Cl: Disseminated patches and plaques, sometimes with blisters, erosions, necrosis, and ulceration. Rapid progression with poor prognosis.

Hi:

- Epidermotropic infiltrate with pagetoid pattern
- Small to medium-sized pleomorphic lymphoid cells
- Necrotic keratinocytes

Immunophenotype: CD3+, CD4–, CD8+, TIA-1+, CD30–, CD45RA+, CD56–.

Genotype : Clonal T-cell receptor rearrangement.

DD: Febrile ulceronecrotic Mucha–Habermann disease.

References

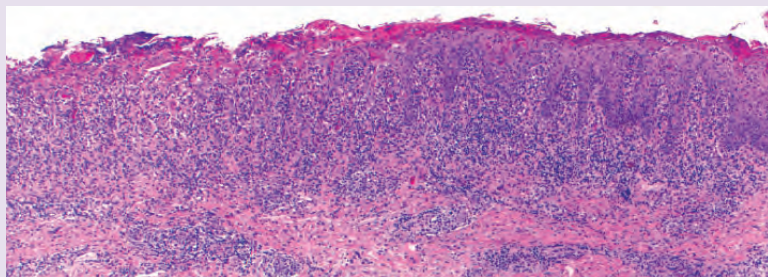
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Differential Diagnosis: Febrile Ulceronecrotic PLEVA (Mucha–Habermann Disease)

Ulceronecrotic plaques

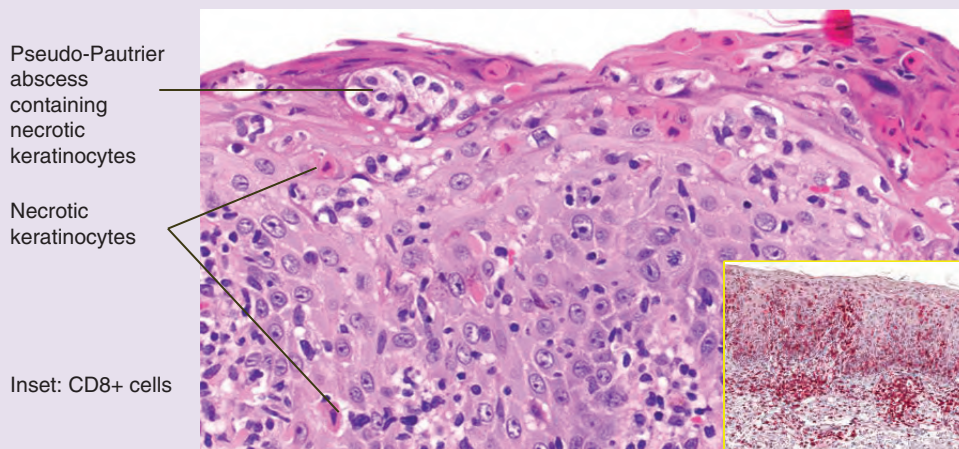


Band-like epidermotropic infiltrate in the upper dermis



PRIMARY CUTANEOUS PERIPHERAL LYMPHOMA (PTL), UNSPECIFIED (NOS)

Differential Diagnosis: Febrile Ulceronecrotic PLEVA (Mucha–Habermann Disease)



Cl: Generalized necrotic plaques, which may merge into large erosions and ulcerations. In addition, there are general symptoms like fever, nausea, diarrhea, and involvement of the central nervous system. The differentiation from aggressive CD8+ epidermotropic T-cell lymphoma (Berti) is obscure.

Hi:

- Epidermotropic lymphoid infiltrate in the upper dermis
- Necrotic keratinocytes

Immunophenotype: CD3+, CD4+, CD8+, CD30–, CD56–, CD57–.

DD: Aggressive CD8+ epidermotropic T-cell lymphoma; pityriasis lichenoides et varioliformis acuta (PLEVA).

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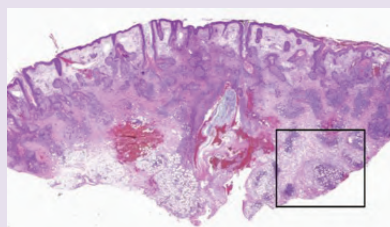
EXTRANODAL NK/T-CELL LYMPHOMA

Extranodal NK/T-Cell Lymphoma, Nasal Type (Subcutaneous)

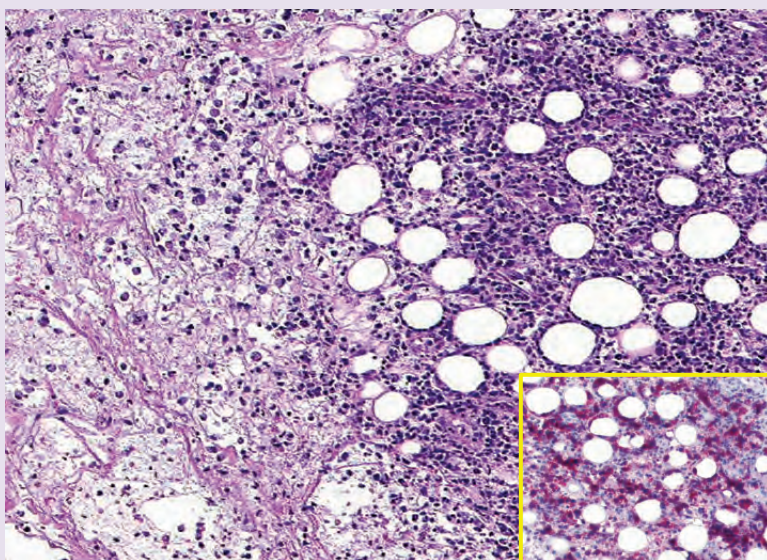
Periorbital
tumorous swelling
(left)

Subepidermal
edema and dense
dermal infiltrate
(right top)

EBER-1+ cells
(right bottom)



CD56+ (inset)
infiltrate
in the subcutis



Cl: Ulcerated plaque or nodule.

Hi: Dermal and subcutaneous infiltrate, composed of small to medium-sized pleomorphic lymphoid cells with angioinvasive growth.

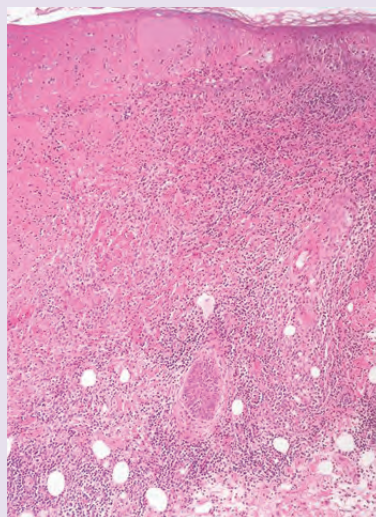
Immunophenotype: CD2+, CD3ε+, CD56+, TIA-1+, granzyme B+, perforin+, EBV+ (EBER).

EXTRANODAL NK/T-CELL LYMPHOMA

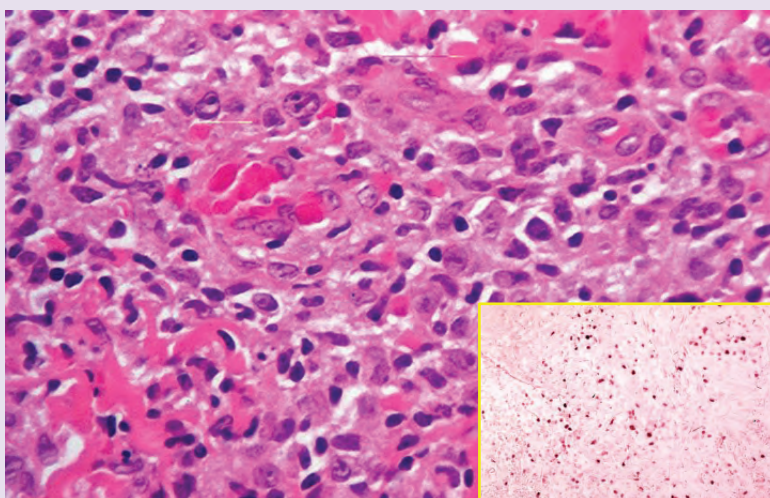
Hydroa Vacciniforme-Like Lymphoma

Swelling of the helix (left)

Dense cellular infiltrate in the dermis and subcutis (right)



Dense (epidermotropic) infiltrate, composed of medium-sized lymphoid cells (EBV+) (inset)



Hydroa-like lymphoma encompasses a group of rare lymphoproliferative disorders of the skin, associated with chronic EBV infection. The oral mucosa may be involved.

CI: Edema, vesiculopapular eruptions, small blisters, crusts, necrotic areas, and scars occur mainly on the nose, ears, and limbs of children and

young adults. The lesions are not induced or exacerbated by UV radiation. There is often high fever, malaise, weight loss, failure to thrive, lymphadenopathy, hepatosplenomegaly, and hypersensitivity to insect bites. Antibodies to EBV can be detected in the serum. Progression to visceral and lymph node involvement.

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Hi:

- Epidermal degeneration and necrosis
- Dense perivascular/periadnexal nodular infiltrate in the dermis and subcutis, with some epidermotropism
- Medium-sized lymphocytes with irregular, hyperchromatic nuclei
- Angiocentric/angiodestructive pattern may be seen in some cases

Immunohistochemistry: CD3+, CD8+, TIA-1+, granzyme B+, CD4−, CD45RO+, CD2+, CD43+, CD5−, CD7−; CD56 is variably expressed; CD30 reactivity can be seen.

Genotype: Clonal rearrangement of the T-cell receptor gene. EBV DNA or RNA sequences are detected by PCR or *in situ* hybridization.

DD: Hydroa vacciniforme; lupus erythematosus.

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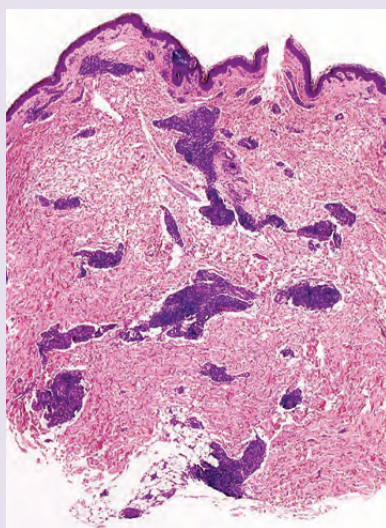
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Angioimmunoblastic T-Cell Lymphoma

Maculopapular eruption on the trunk (left)

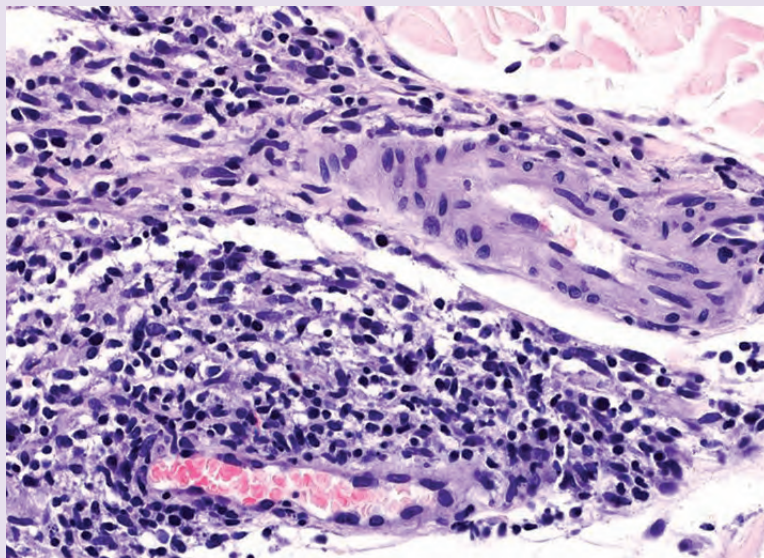
Dense perivascular infiltrates in the dermis (right)



ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Angioimmunoblastic T-Cell Lymphoma

Vascular hyperplasia and pleomorphic lymphoid infiltrate



This systemic malignant lymphoproliferative disorder shows clonal growth of atypical lymphoid cells accompanied by the proliferation of high endothelial venules and follicular dendritic cells.

Cl: Skin involvement occurs in up to 50% of cases, usually in the form of a generalized maculopapular eruption with a predilection for the trunk, mimicking a viral exanthema, drug eruption or erythroderma of any cause. General symptoms include fever, weight loss, night sweats, lymphadenopathy, hepato- and splenomegaly, and polyclonal hypergammaglobulinemia.

Hi: Various types have been differentiated.

- Prominent vascular hyperplasia with epithelioid endothelial cells
- Dense perivascular infiltrates of pleomorphic cells involving superficial and deep dermis
- Reactive infiltrate of mature B-cells, plasma cells, and histiocytes

Immunophenotype: Mature T-helper cells: CD3+, CD4+, CD8+/-, PD-1+, ICOS+, bcl-6+, CD10+, CXCL-13+. Increased number of dermal dendritic cells (factor XIIIa).

Genotype: Clonal TCR gamma gene rearrangement was found in some cases.

DD: Drug reaction; viral exanthema; dermatomyositis; chronic urticaria; purpura fulminans.

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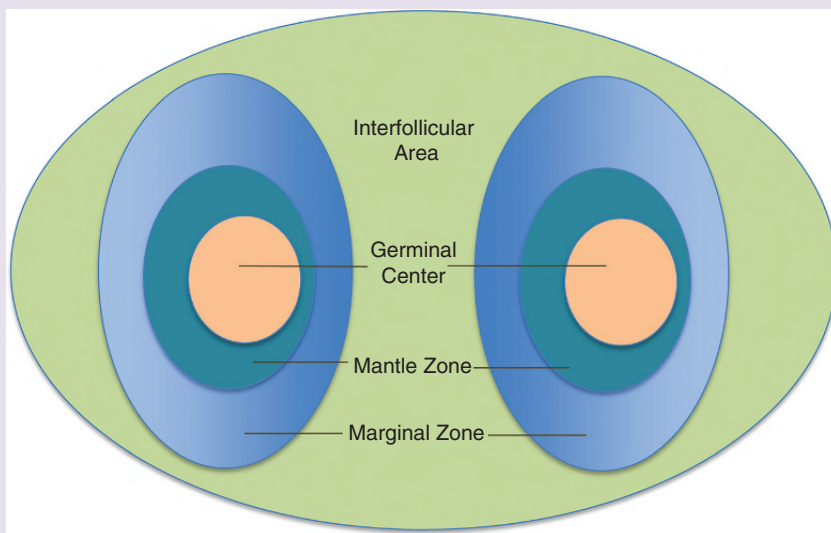
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Cutaneous Mature B-Cell Lymphoid Neoplasms (CBCL)

For the characteristic growth pattern of B-cell infiltrates in the skin, see above.

The skin is a secondary lymphoid organ, to which lymphoid cells home and may organize in a pattern corresponding to the various structures of the reactive lymph follicle: germinal center, mantle zone, marginal zone, and interfollicular area (Table 12.1).

Structure of the Lymph Node



MARGINAL ZONE LYMPHOMA

Table 12.1 Immunophenotypical profiles of some cutaneous B-cell lymphomas.

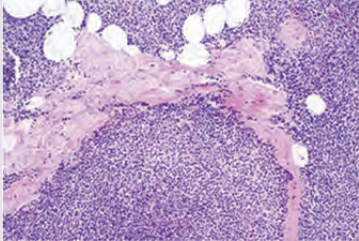
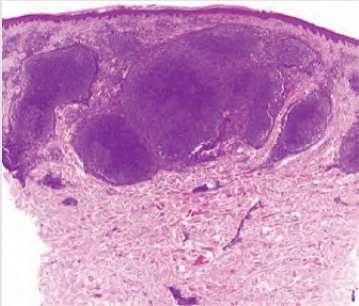
	Bcl-2	Bcl-6	CD 10	t(14;18)	MUM-1 IRF-4	CD 21
MZL/ICY	+	-	-	-	-	+
FCL	-	+	+	-	-	-
DLBCL	+	+	-	+/-	+	-

DLBCL, diffuse large B-cell lymphoma; FCL, follicle center cell lymphoma; MZL/ICY, marginal zone lymphoma/immunocytoma. Red squares indicate diagnostic hallmarks.

Cutaneous Marginal Zone B-Cell Lymphoma (MZL; MALT Type)

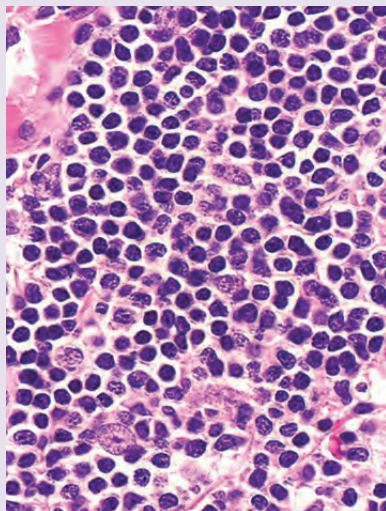
Nodular lesion on the nose (left)

Nodular dermal infiltrates corresponding to B-cell pattern (right top and bottom)

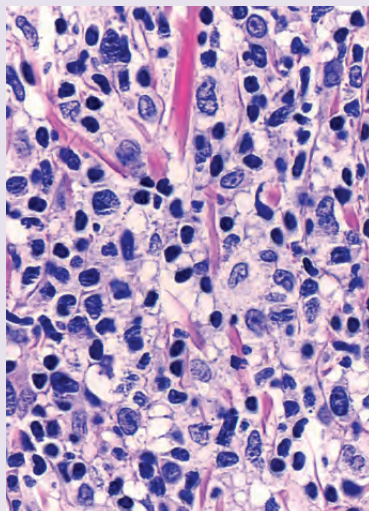


MARGINAL ZONE LYMPHOMA**Cutaneous Marginal Zone B-Cell Lymphoma (MZL; MALT Type)**

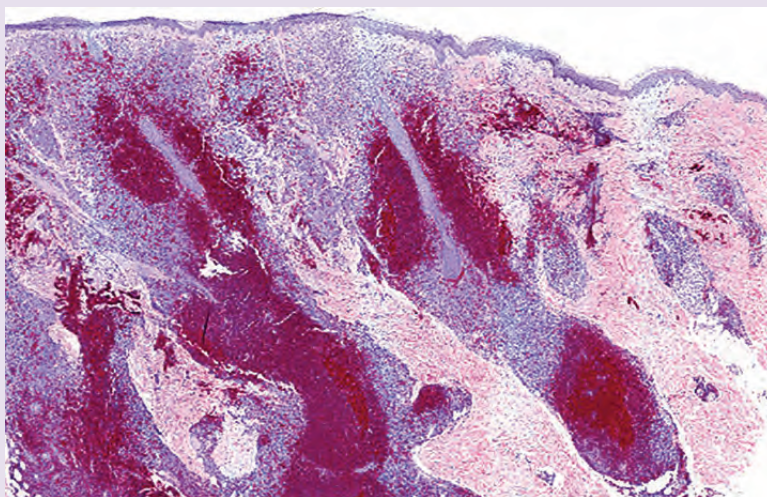
Small
monomorphic
B-cells (left)



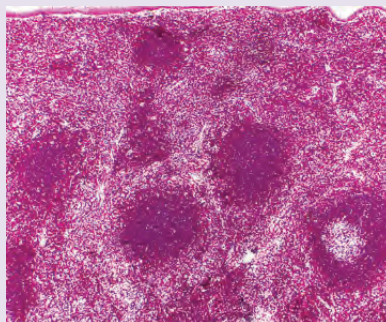
Monocytoid
marginal
zone cells (right)



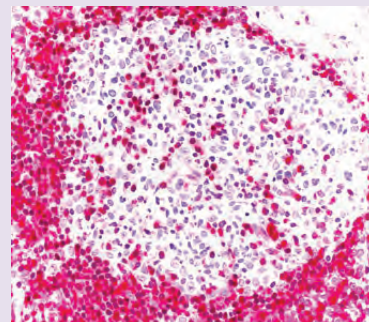
B-cell marker
CD20



Bcl-2+ marginal
zone cells
(left)



Colonisation of
reactive
germinal centers
by bcl-2+
tumor cells
(right)

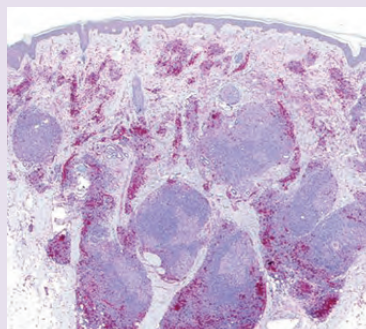
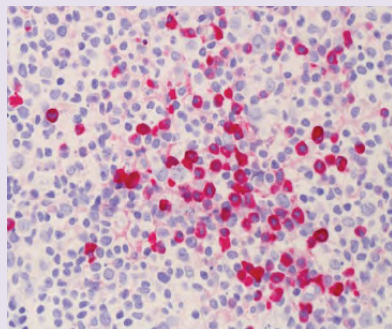


MARGINAL ZONE LYMPHOMA

Cutaneous Marginal Zone B-Cell Lymphoma (MZL; MALT Type)

Lambda positive
monotypic
plasma cells
(left)

CD123+
plasmacytoid
dendritic cells
at the border of
the infiltrates
(right)



Cl: Red to violaceous infiltrated plaques or firm nodules on an erythematous background. In contrast to follicle center cell lymphoma, which is preferentially located on the head and neck, the sites of predilection of MZL are the trunk and arms.

Hi:

- Nodular well-circumscribed infiltrates in the dermis (B-cell pattern)
- Sometimes “inverse pattern” on scanning magnification: darker centers surrounded by brighter zones of pale-staining cells
- Marginal zone cells with reniform nuclei and monocytoid appearance or plasma cell differentiation in the periphery
- Reactive germinal centers
- The cellular population in the interfollicular areas is represented by small lymphocytes, lymphoplasmacytoid cells, and aggregations of plasma cells
- Occasionally, the infiltrate is arranged around adnexal structures analogous to lymphoepithelioid lesions of MALT lymphoma of the gastrointestinal tract

Immunophenotype: Neoplastic cells: CD20+, bcl-2+, bcl-6-, MUM1-; aggregates of monotypic plasma cells; numerous reactive CD3+ T-cells.

DD: Follicle center cell lymphoma; immunocytoma; B-cell pseudolymphoma.

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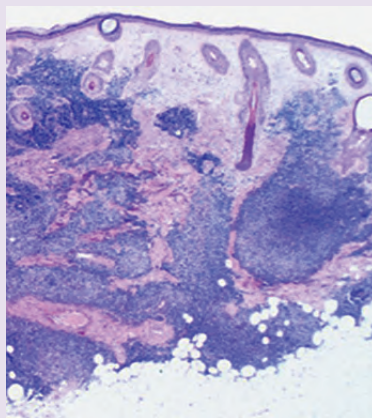
MARGINAL ZONE LYMPHOMA

Variant: Immunocytoma

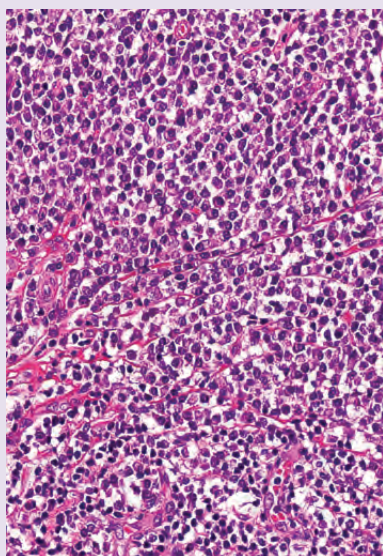
Infiltrated disc-like plaque, several weeks following a tick bite with *Borrelia burgdorferi* infection (left)



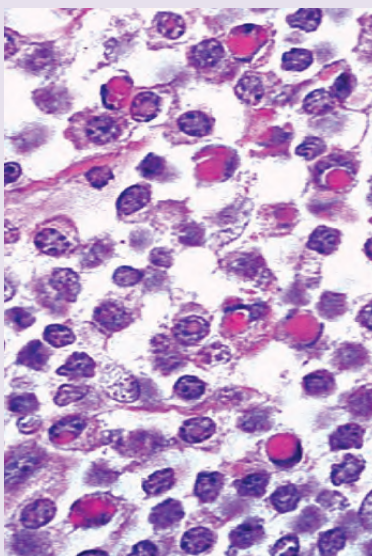
Nodular well demarcated infiltrates in the dermis. Inverted follicular pattern (right)



Small lymphocytes (left)



Plasma cells and lymphoplasmacytoid cells with intranuclear PAS positive Dutcher and Russell bodies (right)



Similar to the pathogenetic role of *Helicobacter pylori* in mucosa-associated lymphoid tumor (MALT), *Borrelia burgdorferi* infection can induce immunocytoma, which is a variant of marginal zone lymphoma, rich in plasma cells.

CI: Mostly solitary infiltrated plaque or tumor. History may reveal infection with *Borrelia burgdorferi*.

Hi:

- Nodular well-demarcated dermal infiltrates (B-cell pattern)
- Predominantly composed of plasma cells and lymphoplasmacytoid cells

- Globular intranuclear inclusions of immunoglobulin in plasma cells and plasmacytoid cells (Dutcher bodies). The number is variable, sometimes very few, and one has to search for them, predominantly in the upper dermis

- Intracytoplasmic inclusions (Russell bodies)

DD: Other cutaneous B-cell lymphomas or pseudolymphomas.

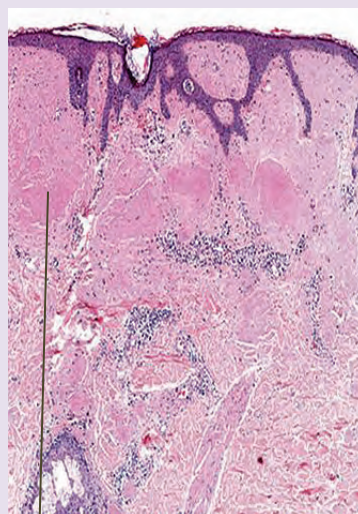
MARGINAL ZONE LYMPHOMA

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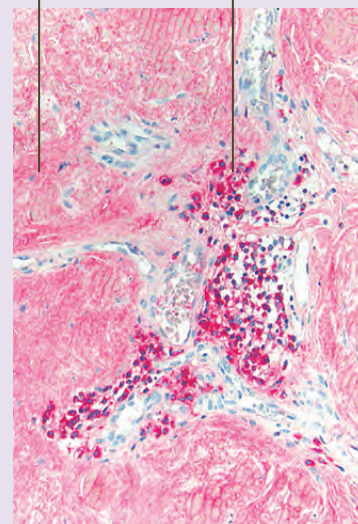
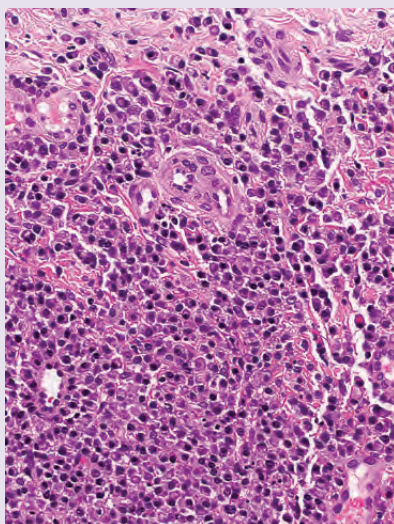
Differential Diagnoses: Multiple Myeloma/Plasmacytoma

Nodular
“metastatic”
lesion in
plasmacytoma
(left and right)



Amyloid
Staining for lambda
light chain

Plasmacytoid
skin infiltrate
(left)



FOLLICLE CENTER LYMPHOMA

Cl: Nodular secondary skin involvement.

Hi: Dermal infiltrates with plasma cells showing light chain restriction. Deposits of AL amyloid may be found.

DD: Other cutaneous B-cell lymphomas; B-pseudolymphomas.

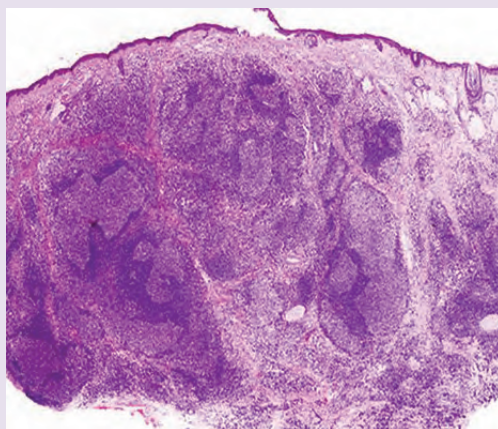
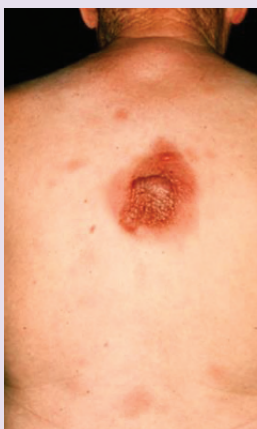
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Becker, M.R., Rompel, R., Plum, J., and Gaiser, T. (2008) Light chain multiple myeloma with cutaneous AL amyloidosis. *J Dtsch Dermatol Ges* 6(9): 744–5.

Primary Cutaneous Follicle Center Lymphoma (FCL)

FCL synonym: "Reticulohistiocytoma of the back [Crosti]" (left)

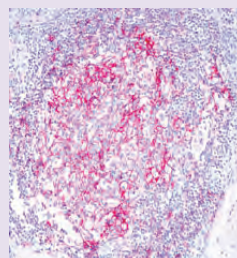
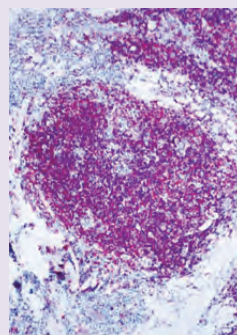
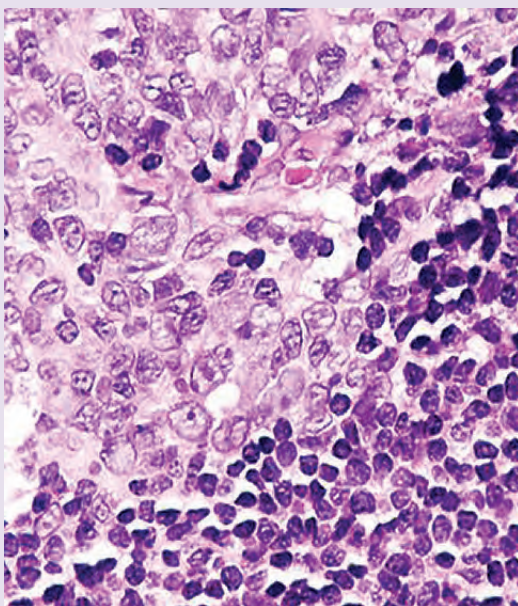
Follicular and diffuse infiltrate in the dermis (right)



Large (centroblasts) and small (centrocytes) follicular center cells (left)

B-cell phenotype of tumor cells: CD79a (right top)

Irregular network of CD21+ follicular dendritic cells (right bottom)



A primary cutaneous B-cell lymphoma with predominance of centrocyte-like tumor cells, which may show a (1) follicular, (2) follicular and diffuse, or (3) diffuse growth pattern. The clinical course is slowly progressive.

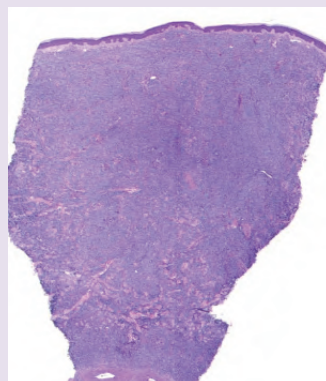
Cl: Solitary, rarely multiple, red-brown nodular lesions or thick plaques with smooth surface on the trunk, head, and neck. Hard consistency is very typical.

FOLLICLE CENTER LYMPHOMA

Primary Cutaneous Follicle Center Lymphoma (FCL)

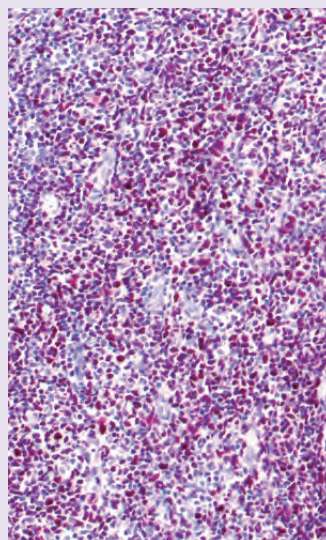
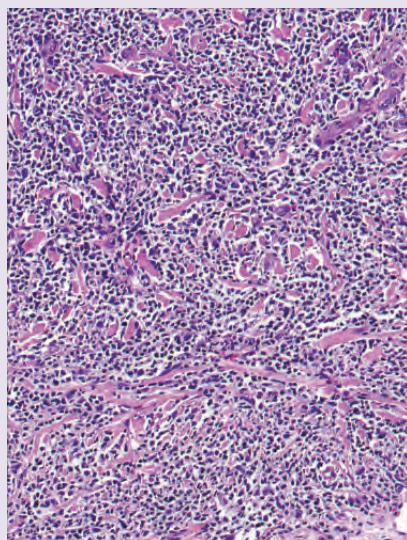
Nodules and tumors on the trunk (left)

Dense diffuse infiltrate throughout the dermis and subcutis. Free subepidermal "grenz-zone"



Dense diffuse infiltrate. Remnants of collagen bundles (left).

BCL6 positive tumor cells (right)

**Hi:**

- Dermal infiltrate (B-cell pattern: no epidermotropism)
- Growth pattern depending on the subtype:
 - Follicular
 - Follicular and diffuse
 - Diffuse
- Lack of polarization, reduced mantle zone
- Mixed large (centroblasts) and small (centrocytes) follicular center cells
- In contrast to marginal zone lymphoma and pseudolymphoma, tingible body macrophages are usually absent
- Irregular networks of follicular dendritic cells (CD21)

Immunophenotype: CD20+, CD79a+, CD10+, bcl-6 +, bcl-2- (90%), MUM-1-; networks of CD21+ follicular dendritic cells.

Genotype: Monoclonal rearrangement of Ig heavy chain genes (80% of cases).

DD: Other cutaneous B-cell lymphomas; B-pseudolymphomas.

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DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Cerutti, P. and Santoianni, P. (1973) A relatively benign reticulosis: Crosti's "reticulohistiocytoma of the back". *Int J Dermatol* **12**(1): 35–40.

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Diffuse Large B-Cell Lymphoma (DLBCL)

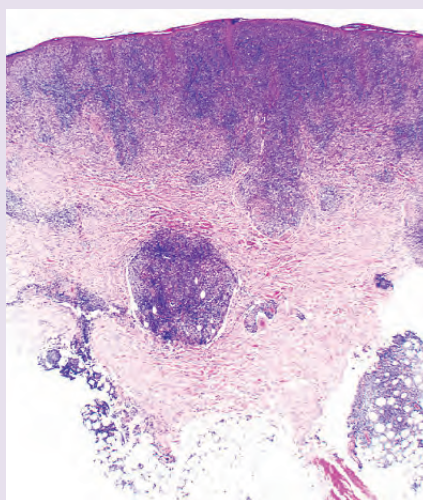
These lymphomas are composed of large B-cells (centroblasts and immunoblasts) and show an aggressive course. DLBCL includes a variety of different entities, formerly referred to as centroblastic lymphoma, immunoblastic lymphoma, "reticulohistiocytoma" or "reticulosarcoma." Two forms of primary cutaneous DLBCL are distinguished in the WHO-EORTC Consensus Classification: DLBCL leg type and DLBCL others. The new WHO classification (2018) has changed "DLBCL, others" to "DLBCL, NOS."

Variant: Cutaneous Diffuse Large B-Cell Lymphoma (Leg Type)

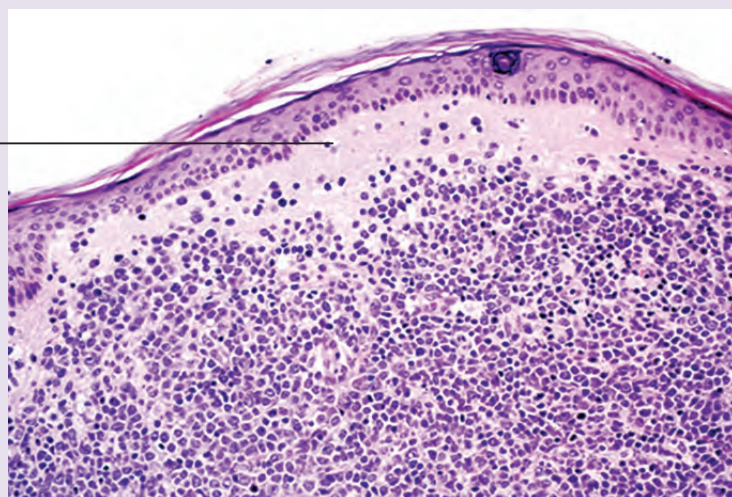
Confluent plaques and nodules on the lower leg (left)



Dense infiltrate in all levels of the dermis and in the subcutis (right)



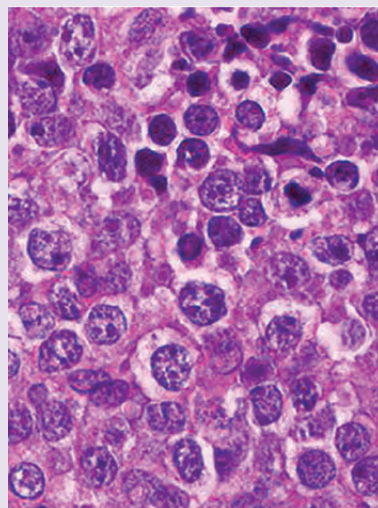
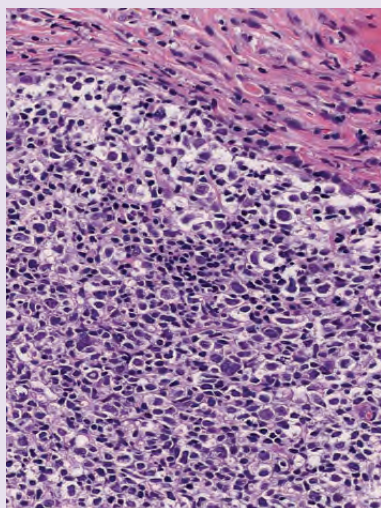
Free Grenz zone



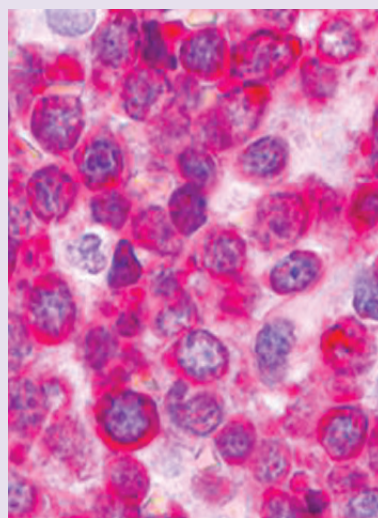
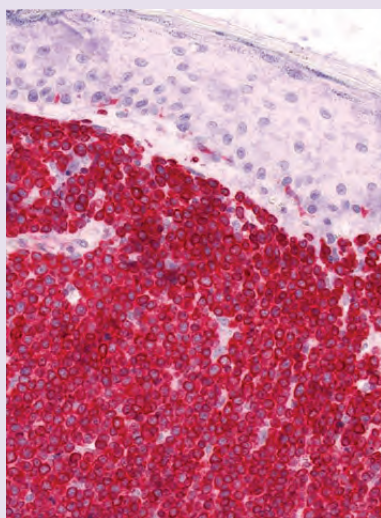
Large lymphoid cells

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Diffuse Large B-Cell Lymphoma (DLBCL)



Large B-cells
(top left and
right) expressing
bcl-2 (bottom
left and right)



CI: Most commonly seen on the lower legs. Rapidly growing solitary or multiple confluent

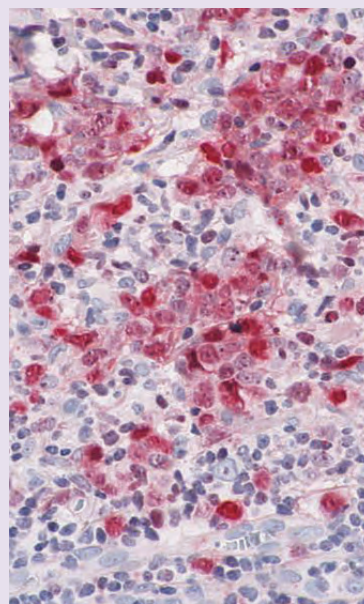
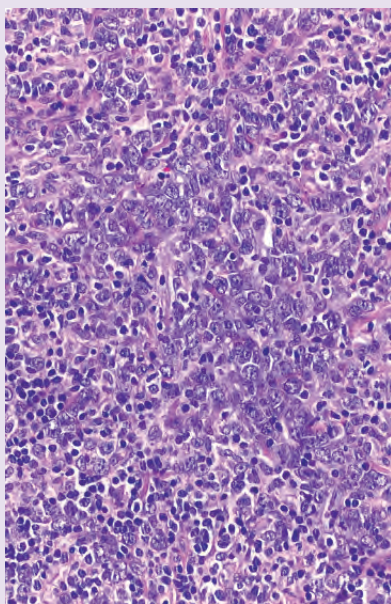
infiltrated plaques or tumors. Smooth surface, sometimes ulcerated.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**Diffuse Large B-Cell Lymphoma (DLBCL), Non-Leg Type**

Arciform infiltrates on the arm



Diffuse large cell infiltrate (left), MUM-1+ (right)



Other localisation (non-leg type) can be involved and basically show the same clinical and histological features.

Hi:

- Diffuse dermal infiltrate, sparing a subepidermal grenz zone
- Large B-cells with abundant cytoplasm:
 - Centroblast: large non-cleaved follicular center cells, showing large vesicular nuclei with small nucleoli attached to the nuclear membrane

- Immunoblasts: large cells with round nuclei and prominent central nucleoli
- Occasionally multilobated, anaplastic or large cleaved cells

Immunophenotype: CD20+ or CD79a+, CD10-/+ , bcl-2+++ , bcl-6+/- , MUM-1/IRF-4++ , IgM+.

Genotype: Monoclonal rearrangement of Ig heavy chain genes.

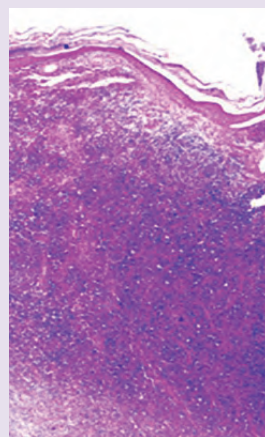
DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

References

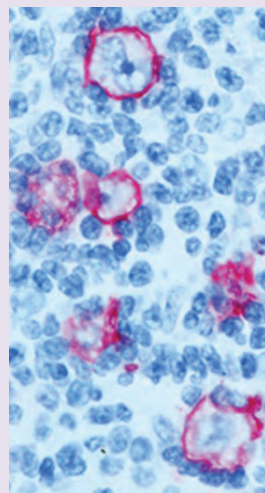
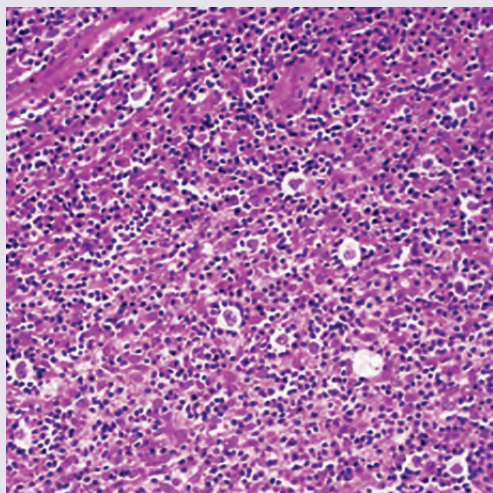
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Variant: T-Cell-Rich B-Cell Lymphoma (DLBCL)

Preauricular infiltrate with superficial ulceration and scarring (left)



Dense infiltrate of T-lymphocytes (top right) with scattered large B-cells (bottom left), expressing CD20 (bottom right)



CD20

This extremely rare variant of a primary cutaneous diffuse large B-cell lymphoma is defined by the predominance (75–90%) of non-neoplastic T-cells admixed with *scattered* tumoral cells expressing B-cell pheno- and genotype.

Cl: Solitary nodule or deep subcutaneous tumor. Multiple lesions are rare. The most frequent site

of involvement is the head and neck area. Association with Gardner's syndrome and with Epstein-Barr virus infection has been reported.

Hi:

- Background of diffuse infiltrate of small lymphocytes expressing T-cell phenotype

- Scattered large pleomorphic tumor cells with clear cytoplasm and multilobular nuclei (starry sky appearance), resembling Hodgkin or Reed–Sternberg cells
- Centroblasts and immunoblasts can be observed
- Marked vascular proliferation is found in some cases

Immunophenotype: Tumor cells bear B-cell markers.

Genotype: Clonal rearrangement of Ig heavy chain genes.

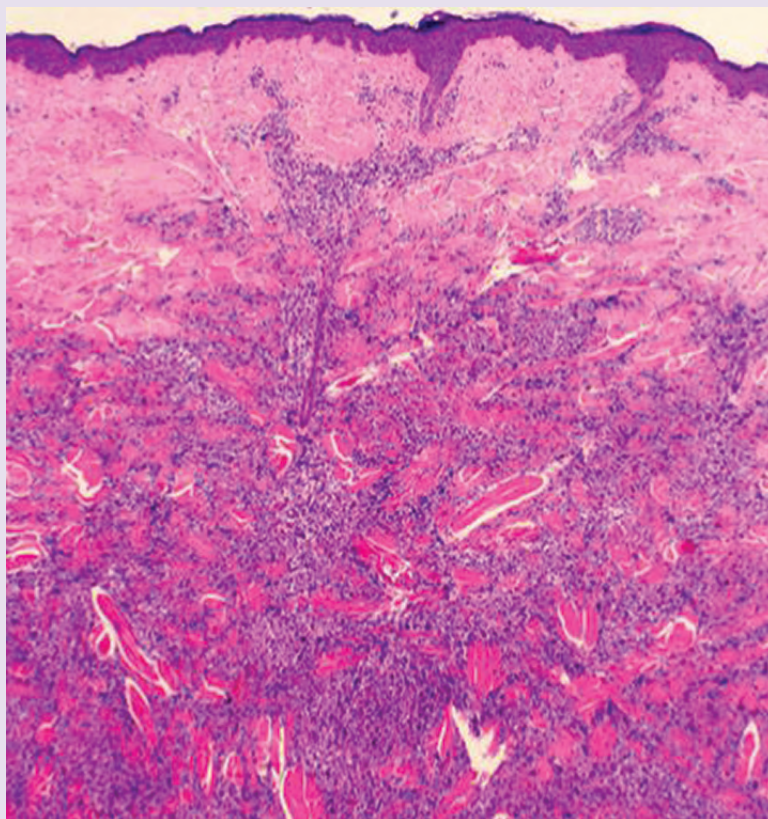
DD: Burkitt's lymphoma; lymphocyte-predominant Hodgkin's lymphoma; small to medium-sized T-cell lymphoma; lymphomatoid granulomatosis.

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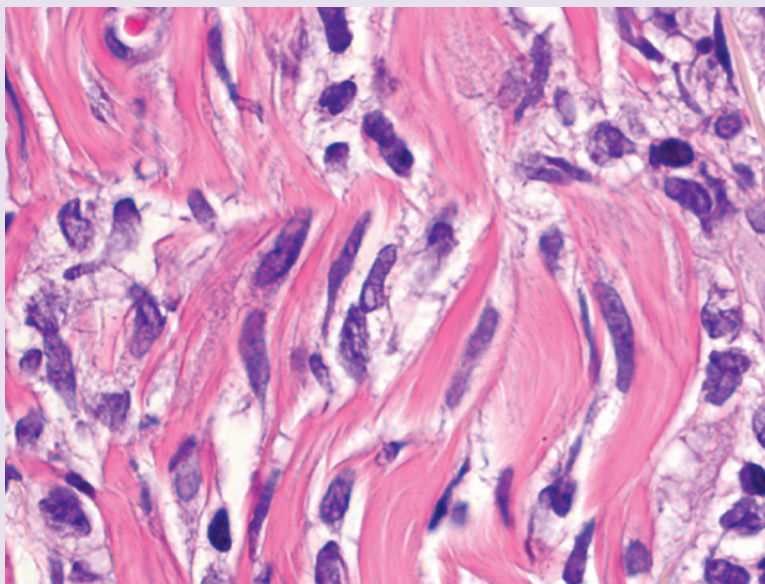
Cutaneous Spindle B-Cell Lymphoma

Diffuse dermal infiltrate without epidermotropism



Cutaneous Spindle B-Cell Lymphoma

Indian filing pattern of spindle-shaped lymphoid cells (expressing B-lymphocyte markers) between collagen bundles



Spindle cell morphology is not a distinct pathognomonic feature designating a specific nosological entity. It is seen as a variant of diffuse large B-cell lymphoma by some authors, but recent molecular studies indicate that it rather represents a form of peripheral cutaneous follicle center lymphoma (PCFCL).

Cl: Inconspicuous plaques or nodular lesions.

Hi:

- Diffuse dense infiltrate in a fascicular pattern
- Spindle-shaped lymphoid cells spreading between collagen bundles

Immunophenotype: CD20+, CD79a+, Bcl-6+, CD10+, CD21+.

Genotype: Clonal rearrangement of Ig heavy chain genes.

DD: Various mesenchymal or epithelial spindle cell tumors.

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EXTRACUTANEOUS B-CELL LYMPHOMA (BCL) WITH FREQUENT SKIN INVOLVEMENT

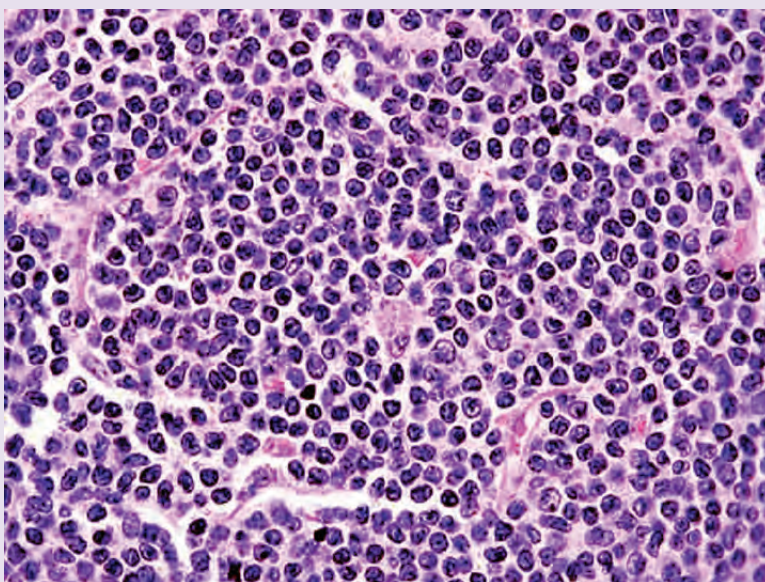
Yun, S.J., Lee, K.H., Yang, D.W., et al. (2009) Primary cutaneous spindle cell B-cell lymphoma with multiple figurate erythema-like manifestation. *J Cutan Pathol* 36(1): 49–52.

Extracutaneous B-Cell Lymphoma (BCL) with Frequent Skin Involvement**Mantle Cell Lymphoma**

Circumscribed infiltrate on the lower leg



Dense proliferation of medium-sized lymphoid cells with irregular angulated nuclei



Lymphomatous proliferation of mantle zone cells in the lymphoid follicles may secondarily involve the skin. However, cases with primary (blastoid) mantle cell lymphoma have been reported.

CI: Inconspicuous plaques and nodules.

Hi:

- Nodular dermal infiltrate
- Grenz zone
- Monotonous proliferation of small to medium-sized lymphoid cells, slightly larger than normal lymphocytes

EXTRACUTANEOUS B-CELL LYMPHOMA (BCL) WITH FREQUENT SKIN INVOLVEMENT

- Irregular angulated or cleaved nuclei, scant pale cytoplasm, dispersed chromatin
- Lymphoblasts may be present in blastic forms of mantle cell lymphoma
- Indian file spreading of tumor cells between collagen bundles

Cytochemistry: Alkaline phosphatase-positive cell membrane.

Immunophenotype: CD20+, bcl-2+, bcl-6-, cyclin D1+.

Genotype: Clonal rearrangement of Ig heavy chain genes; t(11;14).

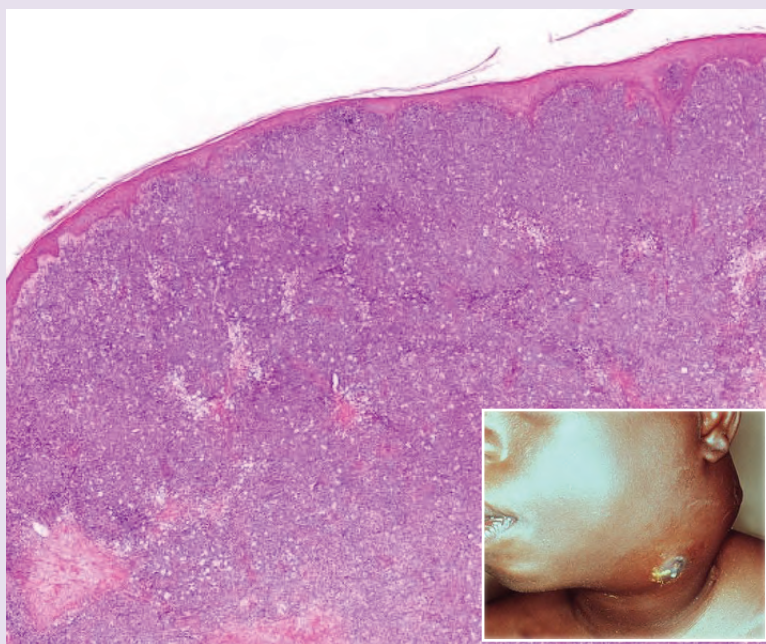
DD: Other B-cell lymphomas.

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Burkitt's Lymphoma (BL)

Cohesive dense dermal infiltrate, per continuitatem from lymph nodes of the neck (inset)

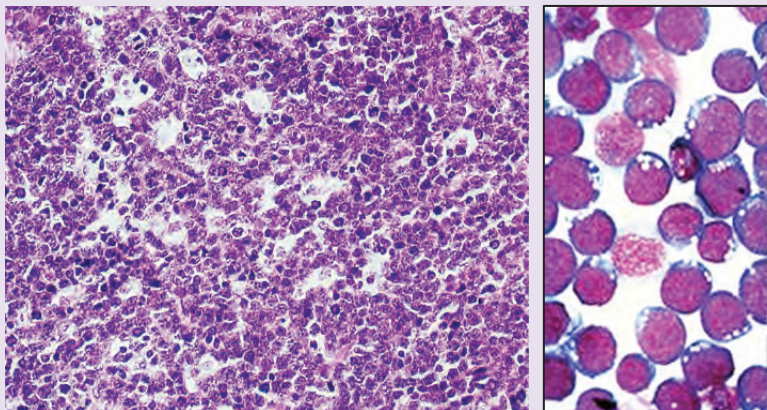


EXTRACUTANEOUS B-CELL LYMPHOMA (BCL) WITH FREQUENT SKIN INVOLVEMENT

Burkitt's Lymphoma (BL)

Monomorphic infiltrate with scattered macrophages, featuring a starry sky pattern (left)

Smear preparation of tumor cells with scant cytoplasm and small vacuoles (right)



Burkitt's lymphoma (BL) is an aggressive B-cell lymphoma, associated with Epstein-Barr virus (EBV) infection in most cases and featuring translocation of the c-myc gene. HIV-induced immunodeficiency may be a predisposing factor.

Cl: The jaws of children in equatorial Africa and sporadically children and young adults in other countries are most commonly affected. Skin may be affected by secondary invasion from regional lymph nodes.

Hi:

- Diffuse cohesive monomorphous non-epidermotropic infiltrate
- Medium-sized lymphoid cells with large nuclei and narrow basophilic cytoplasmatic rim showing small lipid vacuoles
- Many mitotic figures and spontaneous cell death
- Scattered pale macrophages (starry sky pattern), containing ingested remnants of apoptotic tumor cells

Immunophenotype: The tumor cells express B-cell-associated antigens (CD19, CD20, CD22), are positive for CD10 and Bcl-6 (pointing to a germinal center origin), and are negative for CD5, CD23, Bcl-2, and TdT.

Genotype: t(8;14) translocation of the myc gene.

DD: Other B-cell lymphomas and pseudolymphomas; T-cell-rich B-cell lymphoma; lymphocyte-rich Hodgkin's lymphoma.

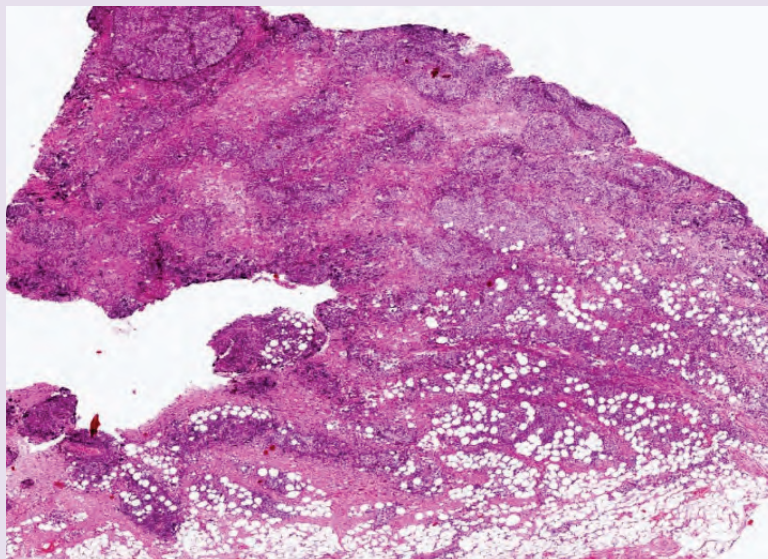
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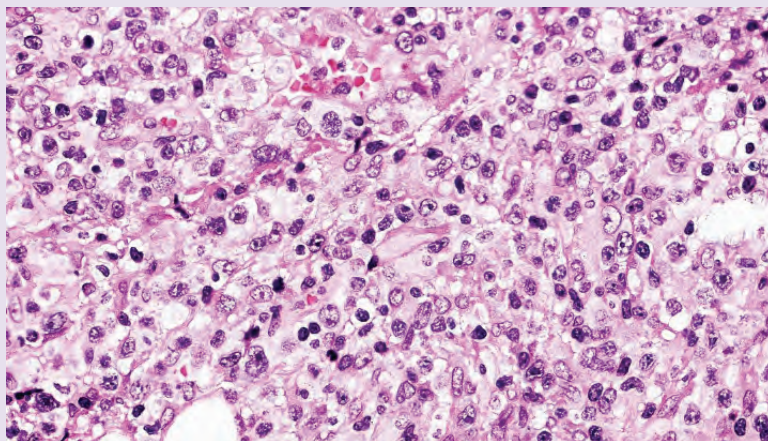
EXTRACUTANEOUS B-CELL LYMPHOMA (BCL) WITH FREQUENT SKIN INVOLVEMENT

Lymphomatoid Granulomatosis (Liebow) (LYG)

Nodular
infiltrate in the
dermis and
subcutis



Polymorphous
lymphohistiocytic
infiltrate.
Destruction of
blood vessels



Lymphomatoid granulomatosis (LYG), originally described by Liebow et al., is a rare multisystemic angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, especially the lungs, skin (in more than 50% of patients), kidneys, and brain. It is EBV positive in most cases and may progress to diffuse large B-cell lymphoma. Although the predominant infiltrating cells are T-cells, the T-cell receptor genes are not clonally rearranged. These findings indicate that LYG is an angiocentric T-cell-rich B-cell lymphoproliferative disorder.

Cl: The clinical features of cutaneous LYG are diverse, transient and manifest as scattered nodules, eroded and crusted lesions, recurrent skin ulcerations, facial edema, papules or folliculitis-like eruptions. EBV infection is an important etiological factor.

Hi:

- Nodular polymorphous lymphohistiocytic infiltrate involving the dermis and subcutis
- Angiocentric and angiodestructive features, inducing necrosis
- No epidermal involvement

INTRAVASCULAR LYMPHOMAS

Immunophenotype: EBV+ in CD20+ B-cells; reactive T-cell infiltrate CD2+, CD3+, CD4+, CD5+, CD7+, CD45RO+.

Genotype: Clonal rearrangement of Ig heavy chain genes.

DD: Vasculitis; other lymphomas.

References

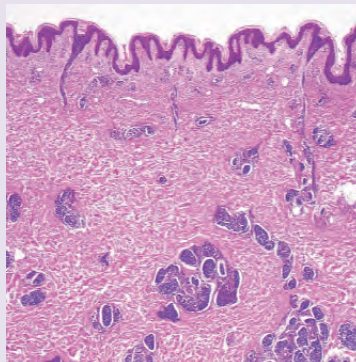
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Intravascular Lymphomas

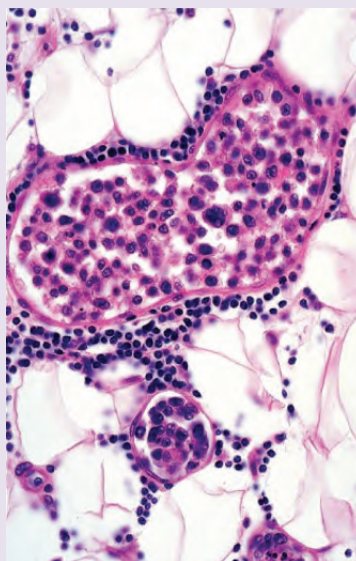
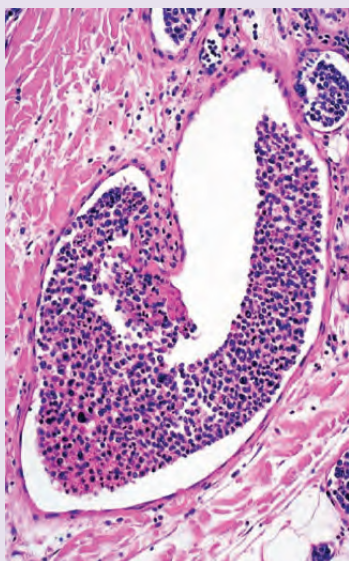
Intravascular Large B-Cell Lymphoma (IV-LBCL) (Systemic Angioendotheliomatosis)

Violet erythemas on the leg (left)

Vessels filled with infiltrating cells (right)



Intravascular pleomorphic cells (left and right)*



Courtesy of Omar P Sanguenza, Winston-Salem/USA

INTRAVASCULAR LYMPHOMAS

Intravascular large B-cell lymphoma is a systemic, diffuse large B-cell lymphoma. Some cases are EBV-associated.

Cl: Erythematous or violaceous plaques or nodules on the face, trunk or lower extremities resembling livedo racemosa.

Hi: Large atypical cells in the lumina of capillaries and venules.

Immunophenotype: B-cell markers.

DD: Reactive angioendotheliomatosis; erythema nodosum; livedo reticularis.

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Intravascular T Cell Lymphoma

Clinical and histological features correspond to the more frequent B-cell variant.

Some cases are EBER positive.

DD: Benign atypical intravascular CD30(+) T-cell proliferation.

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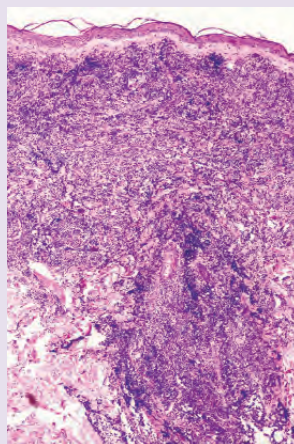
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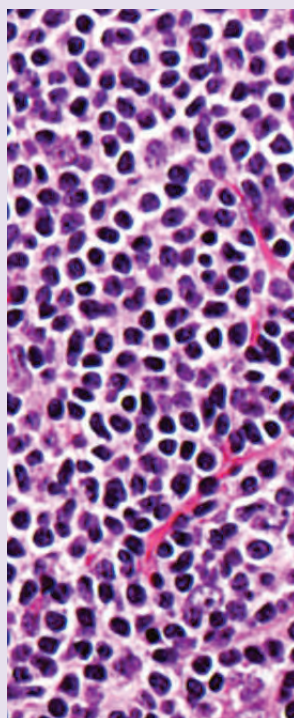
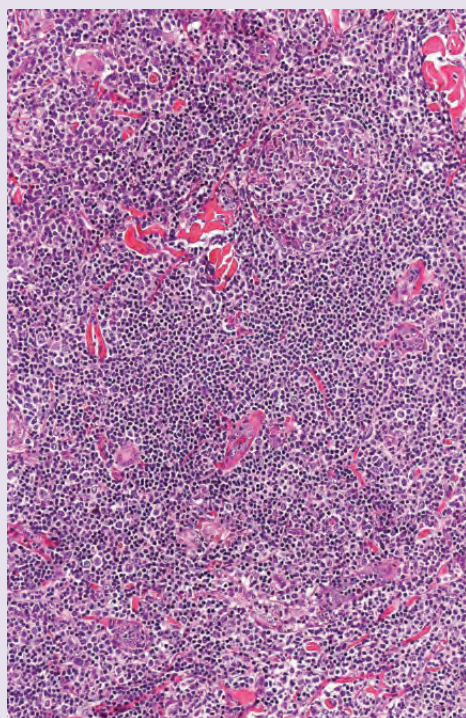
Secondary Skin Involvement in Leukemias/Lymphomas

Chronic Lymphocytic Leukemia (CLL)

Nodular lesions on the forehead



Dense monomorphous infiltrate of small lymphocytes with scant cytoplasm. Sparing of the grenz zone (top right, bottom left and right)



B-CLL is an accumulative disease of long-lived, mature, monoclonal CD5+ B-cells that express high levels of the antiapoptotic protein bcl-2. Specific skin lesions occur in approximately 8% of patients with B-CLL. Many more patients

suffer from non-specific symptoms including purpura, ecchymoses, and maculopapular eruptions.

CL: Specific lesions present as red or violaceous macules, papules or nodules with smooth surface,

preferentially on the face and the ears. Specific infiltrates may be seen at the site of herpes zoster and herpes simplex scars and in association with *Borrelia burgdorferi* infection.

Hi: Dense monomorphous infiltrates of small lymphocytes with chromatin-dense nuclei, small nucleoli, and scant cytoplasm. Variable numbers of eosinophils, neutrophils, and plasma cells may be present.

Immunophenotype: CD19+, CD20+, CD79a+, CD5+, CD23+; monoclonal expression of Ig light chains, sIgM or sIgD.

DD: Cutaneous B-cell lymphomas and pseudolymphomas.

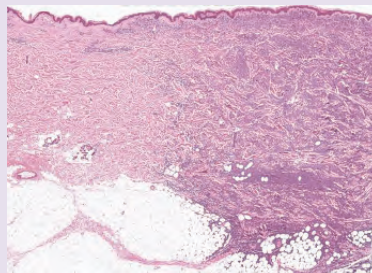
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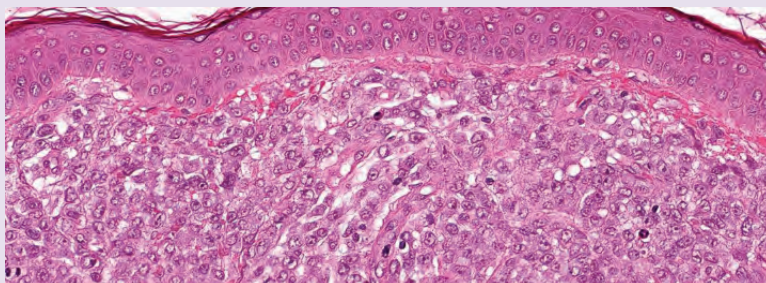
Myeloid and Monocytic Leukemias

Red-brown nodules on the trunk (left)

Diffuse infiltrate in the dermis (right)



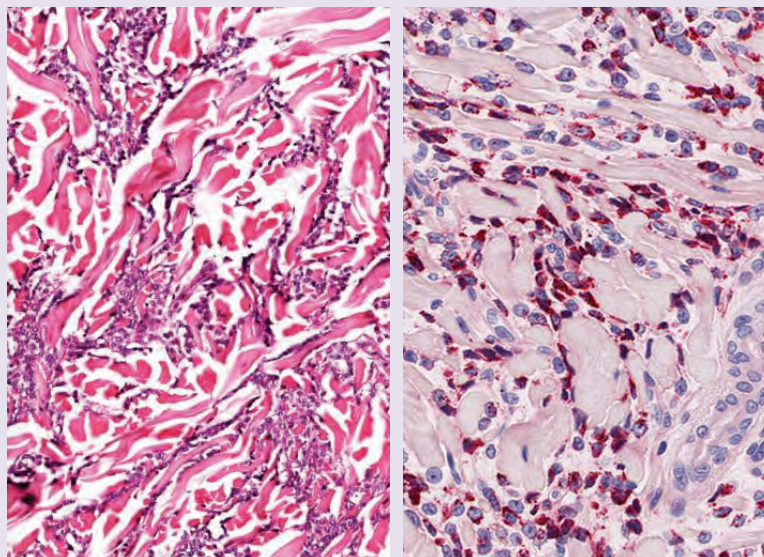
Monocytoid cells



Myeloid and Monocytic Leukemias

Indian filing pattern of tumor cells between collagen bundles (left)

Chloroacetates-terase (Leder) stain of myeloid cells (right)



Cl: In acute myelomonocytic leukemia, mucocutaneous lesions are found in up to 30% of patients. On the skin, they present in a very typical fashion as disseminated red to violaceous thin plaques and papules.

Hi:

- Dense nodular and diffuse pleomorphic infiltrate in the dermis, extending into the subcutis
- Mature and immature cells of the granulocytic series, including atypical myelocytes, eosinophilic metamyelocytes, and neutrophils
- Indian file formation of tumor cells between collagen bundles is very typical

Cytochemistry: Most cells are positive for naphthol-ASD-chloroacetate esterase (Leder stain), lysozyme, and myeloid peroxidase.

Immunophenotype: CD68+, CD14+, MPO+, CD13+, CD33+, CD34+, ERG+, MNDA+, myeloid dendritic cell antigens (BDCA3).

References

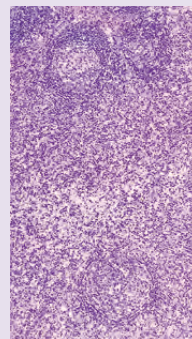
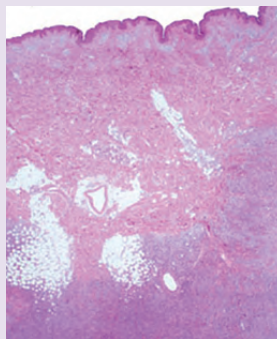
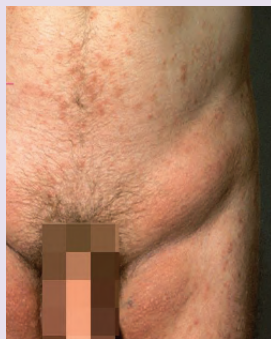
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T-Zone Lymphoma

Papulomacular rash on the abdomen.
Swelling of inguinal lymph nodes (left)

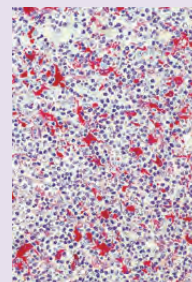
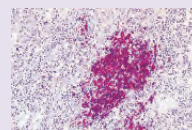
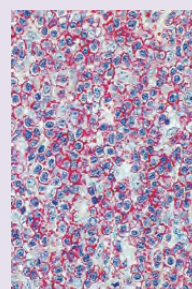
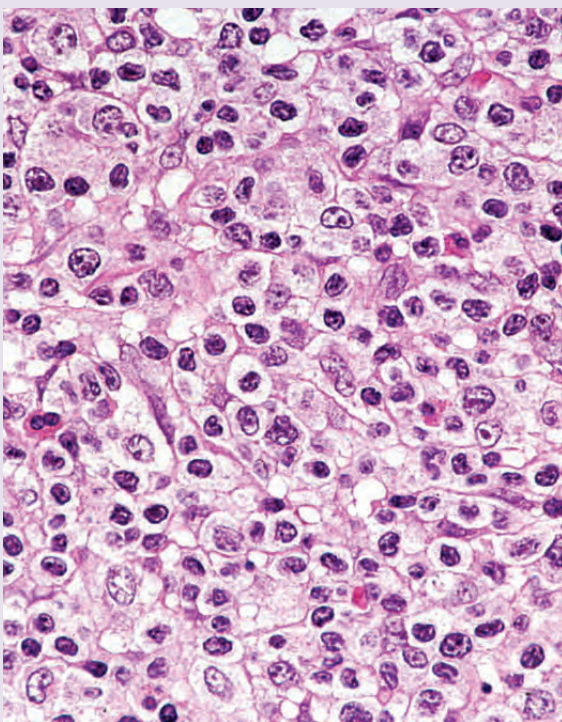
Dense dermal infiltrate (mid)

Lymph node:
proliferation of interfollicular tumor cells between reactive lymph follicles (right)



Pleomorphic "interfollicular" haloed tumor cells with abundant cytoplasm (left)

CD45+ tumor cells (right top).
CD20+ B-cells (right mid).
Factor XIIIa+ dendritic cells (right bottom)



T-zone lymphoma (TZL) is a rare subtype of nodal peripheral T-cell lymphoma characterized by a clonal expansion of T-zone lymphocytes accompanied by a proliferation of other T-zone constituents.

Cl: Non-specific symptoms are frequent but specific lesions are rarely found and may present as widespread papulonodular rash. Peripheral lymph nodes are enlarged.

Hi:

- Diffuse and perivascularly arranged lymphocytic infiltrate in the dermis and subcutis
- Tightly packed, medium-sized pleomorphic lymphocytes with abundant clear haloed cytoplasm

Lymph node: Effaced architecture; interfollicular proliferation of medium-sized lymphocytes with abundant clear cytoplasm. Increased

number of factor XIIIa + dermal dendritic cells and postcapillary venules.

Immunophenotype: CD3+, CD43+, CD45RO+; negative for CD20, CD21, and CD30.

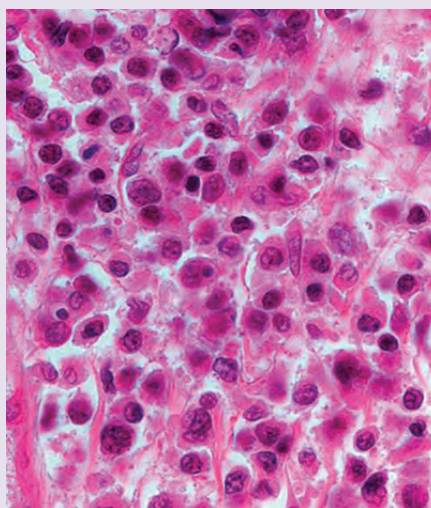
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Adult T-Cell Leukemia/Lymphoma (ATLL)

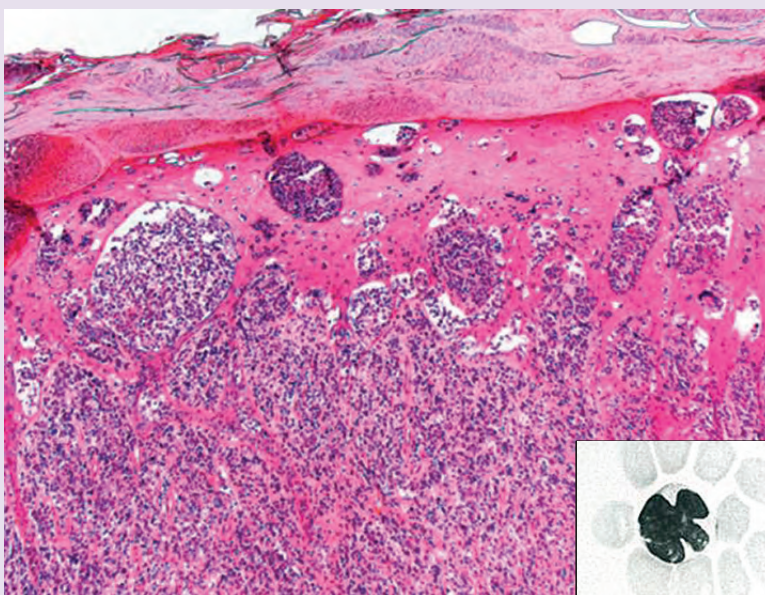
Disseminated erythematous plaques (left)

Medium to large pleomorphic cells (right)



Epidermotropic dermal infiltrate

"Flower cell" in the peripheral blood (inset)



Adult T-cell leukemia/lymphoma is a peripheral T-cell lymphoma, etiologically associated with human T-cell leukemia virus-1 (HTLV-1), which is endemic in south-western Japan and the Caribbean.

CI: Various subtypes can be differentiated: acute, chronic, lymphomatous, and smoldering. Skin involvement occurs in about 50% of cases, presenting as purpuric papules, nodules or tumors, or as erythroderma. Peripheral blood smears show atypical lymphoid cells with polylobulated, convoluted nuclei (so-called flower cells) and leukocytosis, sometimes in conjunction with anemia. Additional findings are hypoalbuminemia, hypergammaglobulinemia, and hypercalcemia.

Hi: Histologically, ATLL shares some features with MF.

- Perivascular or diffuse infiltrate in the upper dermis
- Medium to large pleomorphic cells

- Prominent epidermotropism with formation of large Pautrier microabscesses
- Plasma cells and eosinophils are less frequent than in MF

DD: Mycosis fungoides; anaplastic large cell lymphoma CD30+.

References

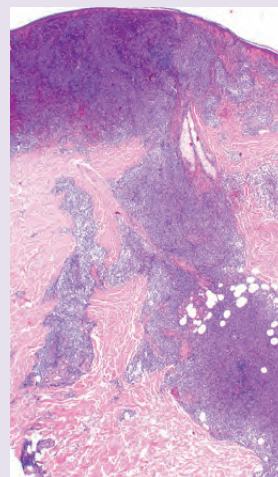
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Immature Hematopoietic Malignancies

Blastic Plasmacytoid Dendritic Cell Neoplasm

Contusiform hemorrhagic plaques (left)

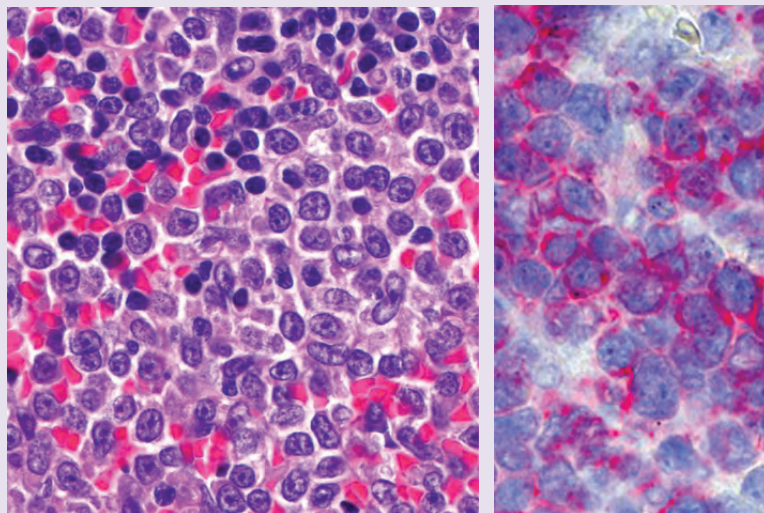
Dermal infiltrate extending to the subcutis (right)



Blastic Plasmacytoid Dendritic Cell Neoplasm

Densely packed blastic tumor cells with irregular nuclei. Erythrocyte extravasation (left)

CD56+ tumor cells (right)



This neoplasm, formerly referred to as CD4+/CD56+ hematodermic blastic NK-cell lymphoma, blastoid NK-cell leukemia/lymphoma or agranular CD4+ CD56+ hematodermic neoplasm, is a tumor of plasmacytoid dendritic cells (CD123+).

Cl: Skin involvement occurs in 87% of cases and manifests with very typical, rapidly growing and expanding contusiform, brownish infiltrated confluent plaques or nodules. The oral mucosa is commonly involved.

Hi:

- Diffuse dermal infiltrates without epidermotropism
- Densely packed, medium-sized and blast-like “lymphoid” tumor cells
- Scant cytoplasm, no granulation
- Irregular nuclei with one or several nucleoli
- Erythrocyte extravasation
- Mitoses are rare
- Few concomitant small T-lymphocytes, no eosinophils or plasma cells

Immunophenotype: CD4+, CD56+, CD123+, BDCA2+, TCL-1+, CD3–, CD8–, TIA-1–, CD34–, CD68–, MPO–, CD1a–, EBV–

Genotype: No clonal rearrangement of T-cell receptor genes or immunoglobulin heavy or light chain genes.

DD: Unique clinical feature: contusiform confluent plaques.

References

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- Garnache-Ottou, F., Feuillard, J., and Saas, P. (2007) Plasmacytoid dendritic cell leukaemia/lymphoma: towards a well defined entity? *Br J Haematol* **136**(4): 539–48.
- Giagounidis, A.A., Heinsch, M., Haase, S., and Aul, C. (2004) Early plasmacytoid dendritic cell leukemia/lymphoma coexpressing myeloid antigens. *Ann Hematol* **83**(11): 716–21.
- Kazakov, D.V., Mentzel, T., Burg, G., Dummer, R., and Kempf, W. (2003) Blastic natural killer-cell lymphoma of the skin associated with myelodysplastic syndrome or myelogenous leukaemia: a coincidence or more? *Br J Dermatol* **149**(4): 869–876.
- Petrella, T., Bagot, M., Willemze, R., (2005) Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol* **123**(5): 662–75.
- Petrella, T., Comeau, M.R., Maynadie, M., et al. (2002) ‘Agranular CD4+ CD56+ hematodermic neoplasm’ (blastic NK-cell lymphoma) originates from a population of CD56+ precursor cells related to plasmacytoid monocytes. *Am J Surg Pathol* **26**(7): 852–62.
- Petrella, T., Dalac, S., Maynadie, M., et al. (1999) CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Francais d’Etude des Lymphomes Cutanes (GFELC). *Am J Surg Pathol* **23**(2): 137–46.

Precursor Lymphoblastic Leukemia/Lymphoma

The skin is not the primary site of manifestation and the diagnosis is based on findings in the lymph nodes, peripheral blood, and bone marrow. B- and T-lymphoblastic leukemia/lymphoma has to be differentiated phenotypically. "Metastatic" nodules in the skin

show monomorphous sheets of atypical immature blast cells with finely dispersed chromatin.

Reference

- Sander, C.A., Medeiros, L.J., Abruzzo, L.V., Horak, I.D., and Jaffe, E.S. (1991) Lymphoblastic lymphoma presenting in cutaneous sites. A clinicopathologic analysis of six cases. *J Am Acad Dermatol* **25**(6 Pt 1): 1023–31.

CHAPTER 13

Cutaneous Cysts

CHAPTER MENU

Cysts with Epithelial Lining

Stratified Squamous Epithelium

Non-Stratified Squamous Epithelium

Cysts without Epithelial Lining (Pseudocysts)

Oral Mucous Cyst and Superficial Mucocele
of the Lip

Digital Myxoid Cyst

Synovial Cyst (Ganglion)

STRATIFIED SQUAMOUS EPITHELIUM

Cutaneous cysts are benign encapsulated firm or fluctuant lesions, containing material of various types. Pseudocysts clinically are similar to cysts but do not have a capsule. Overviews on the various types of cysts and pseudocysts are given in the following papers.

References

- Grosshans, E. and Cribier, B. (1994) [Cutaneous cysts and pseudocysts. I] *Ann Dermatol Venereol* **121**(8): 594–9.
- Grosshans, E. and Cribier, B. (1994) [Cutaneous cysts and pseudocysts. II] *Ann Dermatol Venereol* **121**(9): 647–53.
- Massa, M.C. and Medenica, M. (1985) Cutaneous adnexal tumors and cysts: a review. Part I. Tumors with

hair follicular and sebaceous glandular differentiation and cysts related to different parts of the hair follicle. *Pathol Annu* **20**(Pt 2): 189–233.

- Massa, M.C. and Medenica, M. (1987) Cutaneous adnexal tumors and cysts: a review. Part II Tumors with apocrine and eccrine glandular differentiation and miscellaneous cutaneous cysts. *Pathol Annu* **22**(Pt 1): 225–76.

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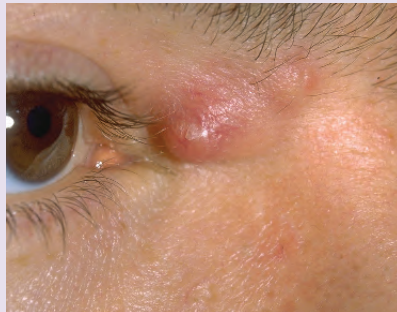
- Thaller, S.R. and Bauer, B.S. (1987) Cysts and cyst-like lesions of the skin and subcutaneous tissue. *Clin Plast Surg* **14**(2): 327–40.

Cysts with Epithelial Lining

Stratified Squamous Epithelium

Epidermal (Infundibular) Cysts

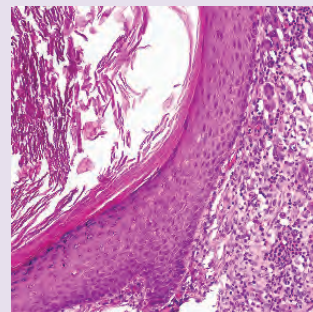
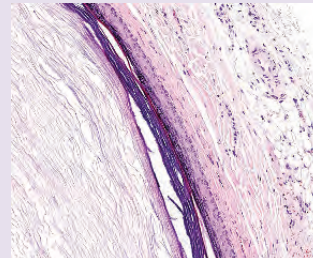
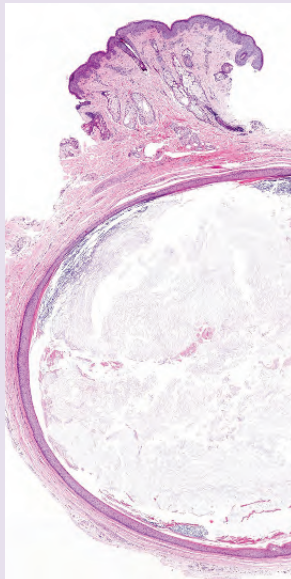
Inflamed cyst (left)



Multilobated cyst (right)



Epidermoid cyst showing infundibular keratinization and loosely packed keratin



Epidermal keratinization and granular layer

STRATIFIED SQUAMOUS EPITHELIUM

This most common cyst is filled with isolated hair shafts and keratinous material (squames) derived from the cornified mural layer. Epidermal cyst is not an “atheroma” but rather a genuine infundibular follicular cyst.

Cl: Round, slowly growing nodule, showing a central pore in some cases. Fixed or slightly movable beyond the overlying erythematous smooth skin surface. Preferred localisations are face, neck, and back. Frequent rupture of the epithelial cyst wall with subsequent bacterial infection leading to abscess formation, bursting, and draining.

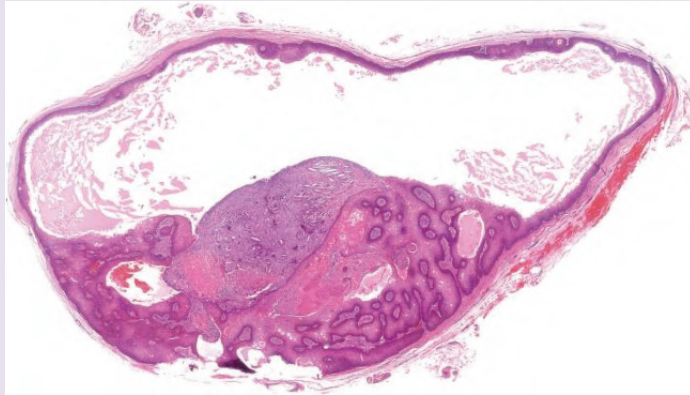
Hi:

- Cyst wall shows flattened epithelium with infundibular-type epidermal keratinization and granular layer
- Basket-weave hyperkeratosis filling the cystic cavity
- Ruptured cysts show suppurative inflammation with granulomatous reaction, followed by fibrosis
- Little or no proliferative activity of the cyst wall epithelium
- Trichilemmal-type focal mural epithelium may be encountered in hybrid cysts

DD: Trichilemmal cyst; cystic adnexal tumor; cystic basal cell carcinoma; cutaneous metastasis.

Variant: Epidermal Proliferating Cyst

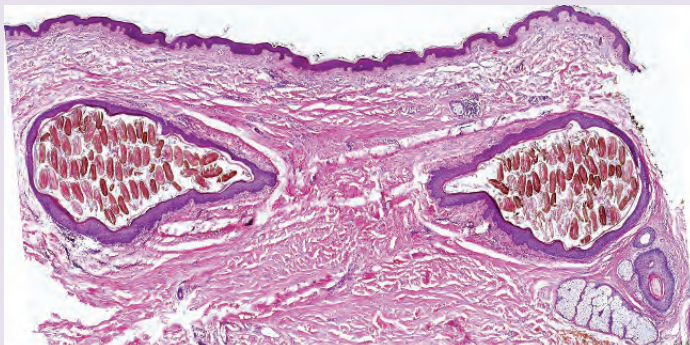
Epidermal cyst with proliferation of squamous epithelium on the bottom of the cyst wall



Hi: Proliferation of squamous epithelium on the bottom of the cyst wall is an unusual feature.

Variant: Epidermal Cyst with Pigment and Vellus Hairs

Epidermal cyst containing vellus hairs and pigment



STRATIFIED SQUAMOUS EPITHELIUM

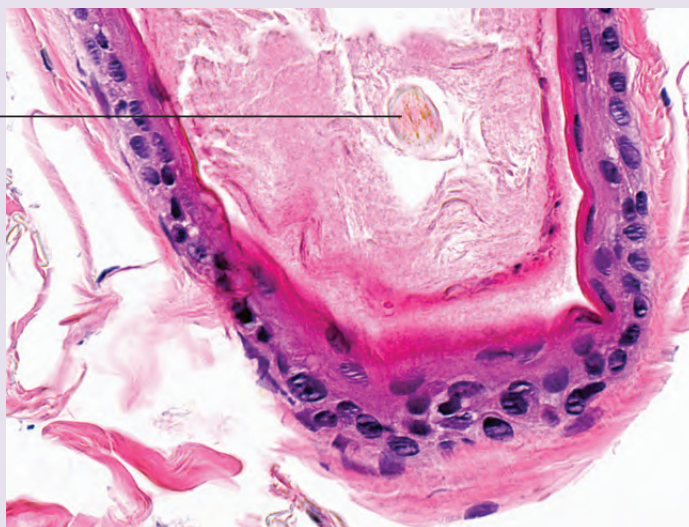
Hi: Vellus hairs and pigment in the cyst cavity.

Vellus Hair Cyst

Tiny papules on the trunk



Thin-walled cyst containing fragments of keratin and a cross sectioned vellus hair



Similar to epidermal cysts, vellus hair cysts arise from the infundibular portion of the hair follicle and contain multiple small vellus hair shafts.

Cl: Multiple tiny papules preferentially on the chest and back, present since birth as part of an autosomal dominant disease (eruptive vellus hair cysts), and manifesting in puberty.

Hi:

- Small thin-walled cyst with stratified squamous epithelium, filled with densely packed keratinous masses (squames)

- Multiple small vellus hair shafts within the cyst
- DD:** Steatocystoma; adnexal tumors.

References

- Ahn, S.K., Chung, J., Lee, W.S., Lee, S.H., and Choi, E.H. (1996) Hybrid cysts showing alternate combination of eruptive vellus hair cyst, steatocystoma multiplex, and epidermoid cyst, and an association among the three conditions. *Am J Dermatopathol* **18**(6): 645–9.

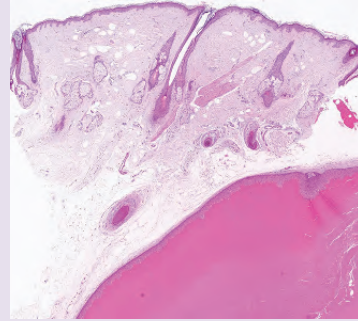
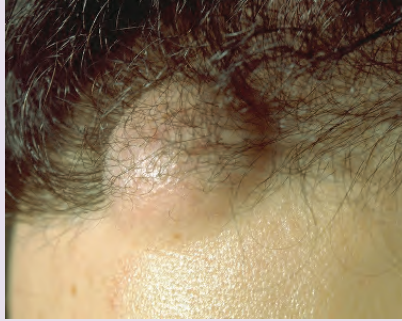
STRATIFIED SQUAMOUS EPITHELIUM

Plewig, G. (1990) Eruptive vellus hair cysts. A follicular cyst of the sebaceous duct (sometimes). *Am J Dermatopathol* **12**(5): 538–9.

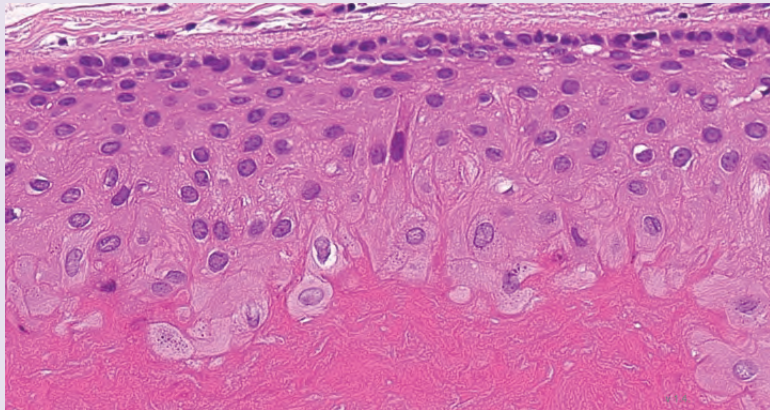
Sanchez Yus, E. and Requena, L. (1990) Eruptive vellus hair cyst and steatocystoma multiplex. *Am J Dermatopathol* **12**(5): 536–7.

Trichilemmal (Isthmus-Catagen) Cyst

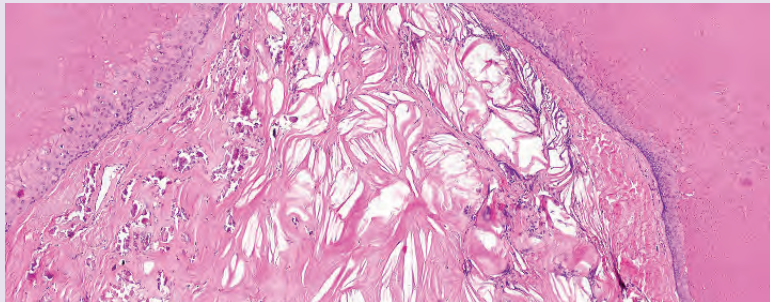
Firm nodule on the scalp



Trichilemmal keratinization. No granular layer. Abrupt transition to densely packed keratin



Granulomatous inflammation and cholesterol clefts



Arising mostly from the isthmus of anagen hair.

Cl: Solitary or multiple mobile firm, sometimes calcifying nodule(s) preferentially on the scalp (90%), face, back, and anogenital region.

Hi:

- Cyst wall consisting of pale stratified squamous epithelial layer

- No granular layer
- Abrupt transition between epithelial cells and homogeneous pale eosinophilic keratinous masses, filling the lumen of the cyst
- Dystrophic calcification, inflammatory granulomatous reaction, cholesterol crystals (clefts), and foamy macrophages are sometimes found

STRATIFIED SQUAMOUS EPITHELIUM

Immunohistochemistry: Epithelial layer showing strong positivity for CK17 and calretinin.

DD: Epidermal cyst; adnexal tumors; proliferating trichilemmal tumor.

References

Ivan, D., Bengana, C., Lazar, A.J., Diwan, A.H., and Prieto, V.G. (2007) Merkel cell tumor in a trichilemmal cyst: collision or association? *Am J Dermatopathol* **29**(2): 180–3.

Nakamura, T. (2011) Comparative immunohistochemical analyses on the modes of cell death/keratinization in epidermal cyst, trichilemmal cyst, and pilomatrixoma. *Am J Dermatopathol* **33**(1): 78–83.

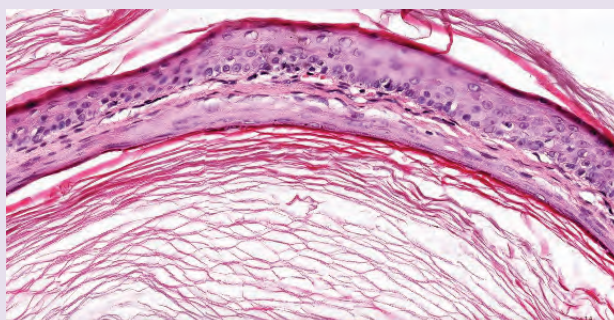
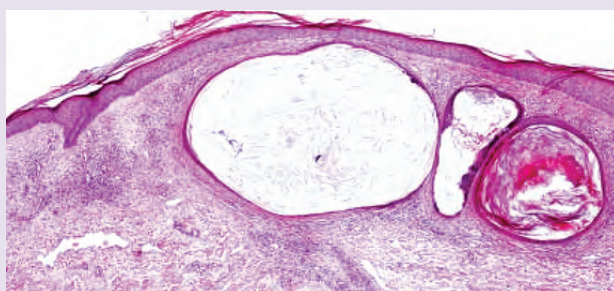
Su, W., Kheir, S.M., Berberian, B., and Cockerell, C.J. (2008) Merkel cell carcinoma in situ arising in a trichilemmal cyst: a case report and literature review. *Am J Dermatopathol* **30**(5): 458–61.

Milia

Multiple milia following blister formation in a patient with porphyria cutanea tarda



Epidermal cysts, filled with amorphous or lamellated masses of keratin (mid and bottom)



STRATIFIED SQUAMOUS EPITHELIUM

Milia are tiny epidermal cysts arising from the infundibular portion of vellus hairs or dermal sweat ducts, without connection to the overlying epidermis.

Cl: Primary milia temporarily present as yellowish tiny papules in the face of infants. They usually disappear within a few weeks. Secondary milia occur in the aftermath of blistering dermatoses (e.g. porphyria cutanea tarda, dystrophic epidermolysis) or after superficial wounds.

Hi:

- Cyst wall with stratified squamous epithelium
- Cyst lumen filled with keratinous material
- Often connected to a vellus hair follicle

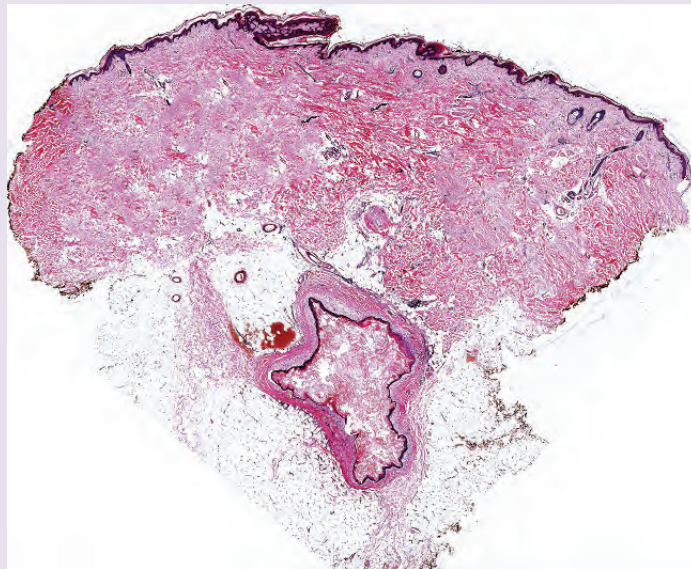
DD: Tiny adnexal tumors; steatocystoma; vellus hair cyst.

References

- Cho, S.H., Cho, B.K., and Kim, C.W. (1997) Milia en plaque associated with pseudoxanthoma elasticum. *J Cutan Pathol* **24**(1): 61–3.
- Terui, H., Hashimoto, A., Yamasaki, K., and Aiba, S. (2016) Milia en plaque as a distinct follicular hamartoma with cystic trichoepitheliomatous features. *Am J Dermatopathol* **38**(3): 212–17.

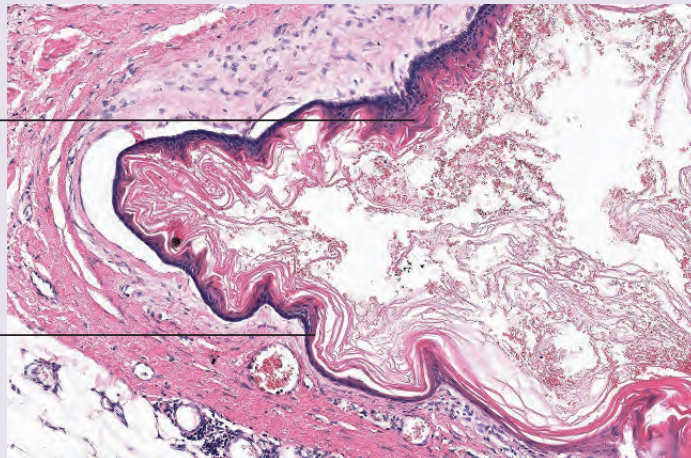
Follicular Hybrid Cyst

Cyst in the subcutis



Trichilemmal keratinization

Infundibular keratinization



STRATIFIED SQUAMOUS EPITHELIUM WITH SWEAT GLAND COMPONENTS: HIDROCYSTOMA

Follicular hybrid cyst shows combined features of both infundibular and trichilemmal keratinization in different portions of the cyst.

Cl: Cystic lesions, preferentially localized on the face.

Hi:

- Infundibular keratinization in one portion of the cyst
- Trichilemmal keratinization in another portion of the cyst
- Abrupt transition from infundibular to trichilemmal keratinization

DD: Pilar cyst; epidermal cyst.

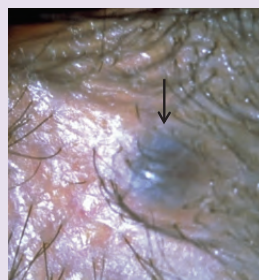
References

- Dargent, J.L., Aupaix, F., and Herin, M. (2013) Follicular hybrid cyst with isthmic-catagen, pilomatrical, and syringocystadenoma papilliferum components. *Am J Dermatopathol* **35**(3): 399–400.
- Miyake, H., Hara, H., Shimojima, H., and Suzuki, H. (2004) Follicular hybrid cyst (trichilemmal cyst and pilomatricoma) arising within a nevus sebaceus. *Am J Dermatopathol* **26**(5): 390–3.
- Requena, L. and Sanchez Yus, E. (1991) Follicular hybrid cysts. An expanded spectrum. *Am J Dermatopathol* **13**(3): 228–33.

Hidrocystoma (Cystadenoma)

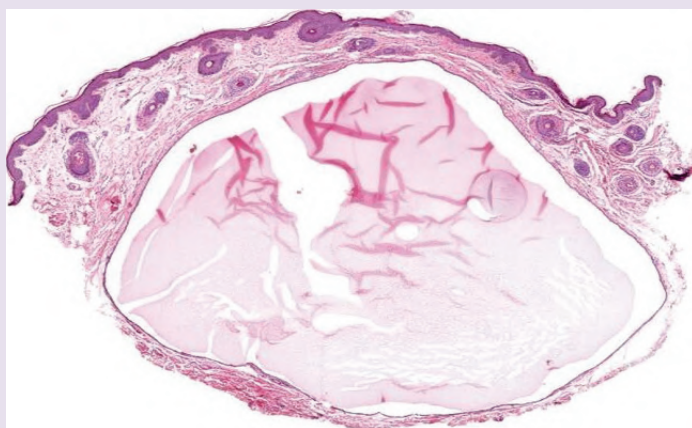
Variant: Eccrine Cystadenoma

Small cysts on the forehead

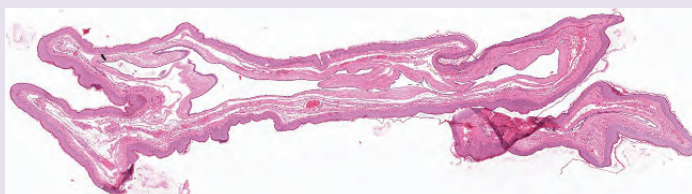


Variant hidrocystoma noire (arrow)

Cyst with eosinophilic debris

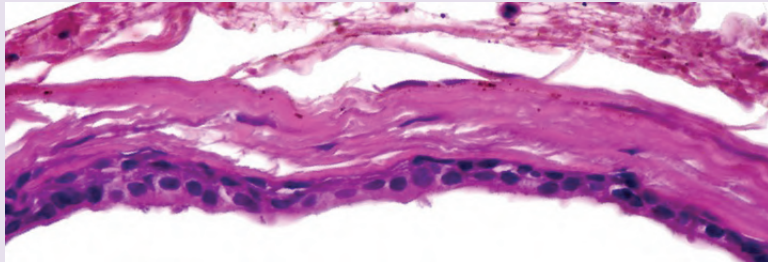


Collapsed cyst

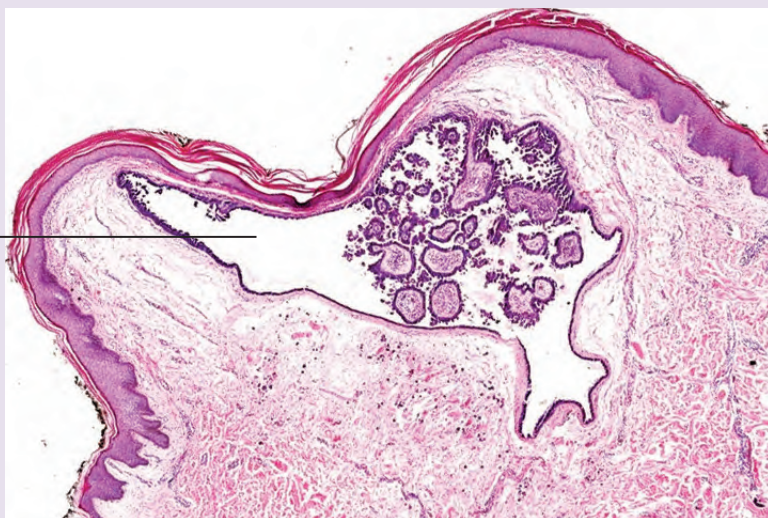


**STRATIFIED SQUAMOUS EPITHELIUM WITH SWEAT GLAND COMPONENTS:
HIDROCYSTOMA****Variant: Eccrine Cystadenoma**

Cyst wall with
two layers of
cuboidal cells

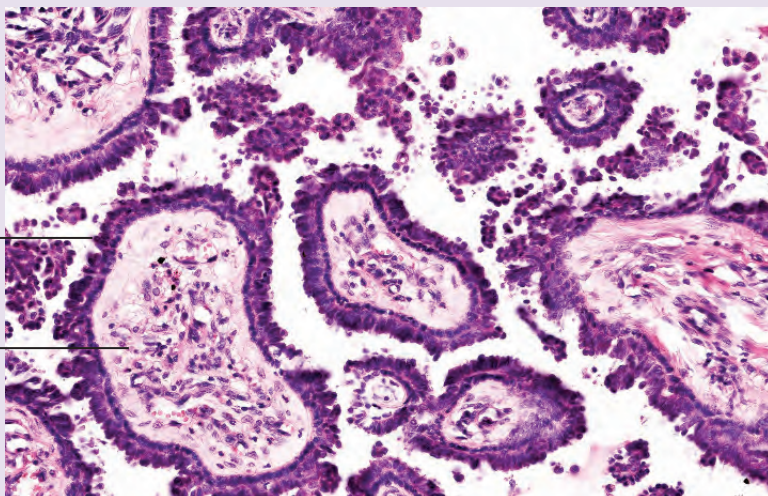


Cystic lesion
with intraluminal
papillary
projections
(papillae and
pseudo-papillae)



Decapitation
secretion

Papilla with
fibrovascular
stroma



STRATIFIED SQUAMOUS EPITHELIUM WITH SWEAT GLAND COMPONENTS: HIDROCYSTOMA

Hidrocyستomas may contain eccrine or apocrine components or both in the cystic wall of stratified squamous epithelium.

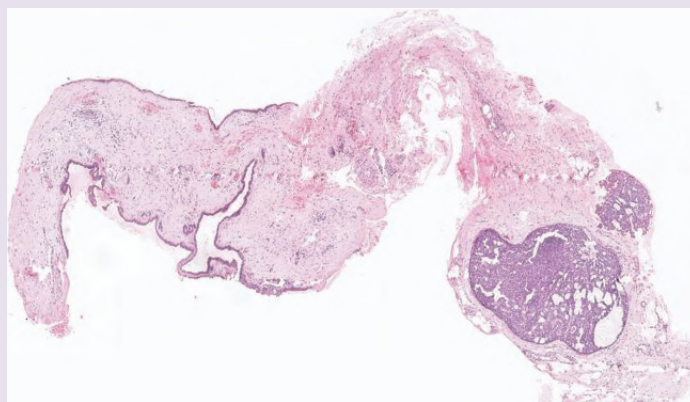
Cl: Solitary or multiple intradermal cystic lesions. Location: face or scalp. Lipofuscin-filled “hidrocystome noire” may simulate nodular malignant melanoma due to the blue-black color of intracystic pigment (Tyndall effect).

Hi:

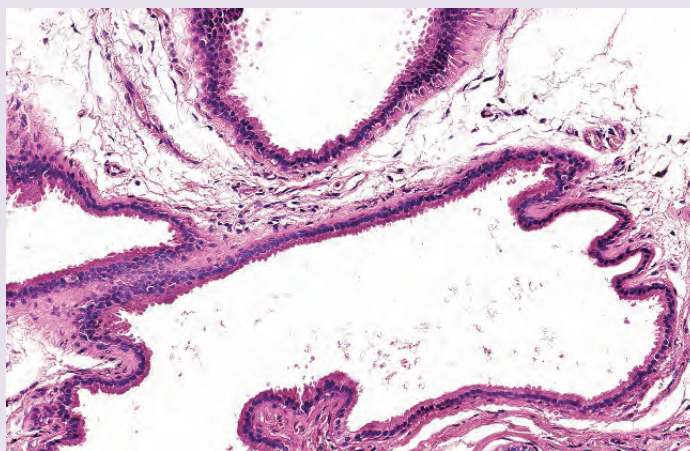
- Cystic cavity may be dilated or collapsed
- Cyst wall lined with secreting epithelium with double layer of cuboidal cells
- Eccrine or apocrine secretion
- Intraluminal papillary projections
- Cyst cavity empty or filled with amorphous eosinophilic masses or dark lipofuscin pigment

Variant: Apocrine Cystadenoma

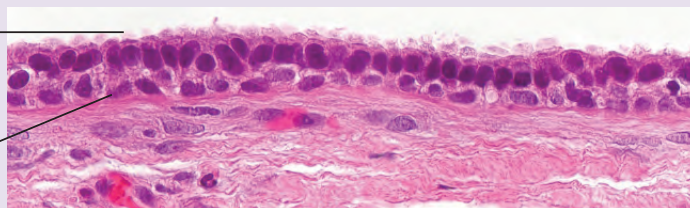
Fragment with solid and cystic components from the eyelid



Papillary formation. Edematous stroma



Double-layered cyst wall



STRATIFIED SQUAMOUS EPITHELIUM

Cl: This small solitary translucent cystic lesion is typically located in the periorbital area (eyelid). Lesions on the penis with similar morphological features are known as median raphe cysts.

Hi:

- Dilated cyst, sometimes with intracystic papillary formations
- Combination of papilla (with stroma) and pseudopapillae (epithelial mounts without stroma)
- Epithelial cyst wall consists of:
 - inner layer of cuboidal cells with decapitation secretion
 - outer layer, consisting of myoepithelial cells
- Edematous or compact stroma

DD: Digital papillary adenocarcinoma (aggressive digital papillary adenocarcinoma) is an invasive adnexal carcinoma on palms and soles simulating a benign apocrine cystadenoma. Hallmarks are cystic structures with a double layer of apocrine epithelia on the inside and a contiguous outer layer of myoepithelia ("*in situ*" type of adenocarcinoma). There is a marked

combination of solid and cystic parts, with papillae and pseudopapillae in the latter. Pleomorphism may be moderate. Proliferative activity and mitoses are conspicuous features. Pathologists should be aware that a proliferative apocrine hidrocystoma or cystadenoma on palms and soles in most cases represents a digital papillary adenocarcinoma.

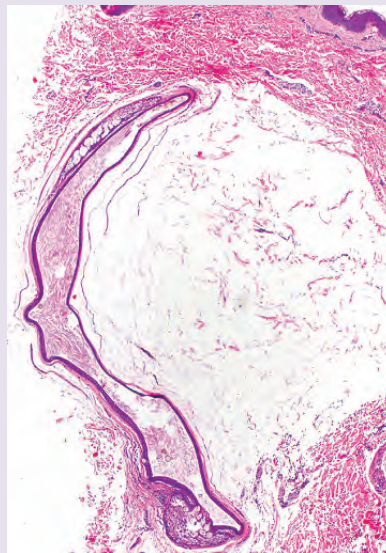
References

- Molina-Ruiz, A.M., Llamas-Velasco, M., Rutten, A., Cerroni, L., and Requena, L. (2016) "Apocrine hidrocystoma and cystadenoma"-like tumor of the digits or toes: a potential diagnostic pitfall of digital papillary adenocarcinoma. *Am J Surg Pathol* **40**(3): 410–18.
- Sugiyama, A., Sugiura, M., Piris, A., Tomita, Y., and Mihm, M.C. (2007) Apocrine cystadenoma and apocrine hidrocystoma: examination of 21 cases with emphasis on nomenclature according to proliferative features. *J Cutan Pathol* **34**(12): 912–17.
- Yanagi, T., Sawamura, D., Nishie, W., Abe, M., Shibaki, A., and Shimizu, H. (2006) Multiple apocrine hidrocystoma showing plane pigmented macules. *J Am Acad Dermatol* **54**(2 Suppl): S53–4.

Steatocystoma, Multiplex and Simplex

Small nodules on the chest (left)

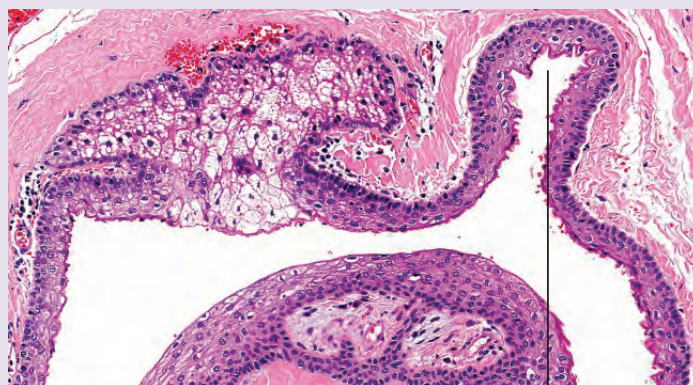
Collapsed cyst (right)



STRATIFIED SQUAMOUS EPITHELIUM

Steatocystoma, Multiplex and Simplex

Sebaceous gland
in cyst-wall



Typical crenellated inner layer of epithelial cyst wall

While steatocystoma multiplex is an autosomal dominant inherited disease, steatocystoma simplex is not. Lesions manifest in puberty. They are considered to be hamartomas of the pilar-sebaceous structure.

Cl: Yellowish or skin-colored round nodules, preferentially located in the sternal region, axilla, arms or genital area.

Hi:

- The cyst wall shows a characteristically wavy (crenellated) luminal surface
- Flat sebaceous glands within the cyst wall
- The cyst may be collapsed, and contain lipids and keratinous material

Immunohistochemistry: Marked expression of calretinin in the upper crenellated epithelial layer.

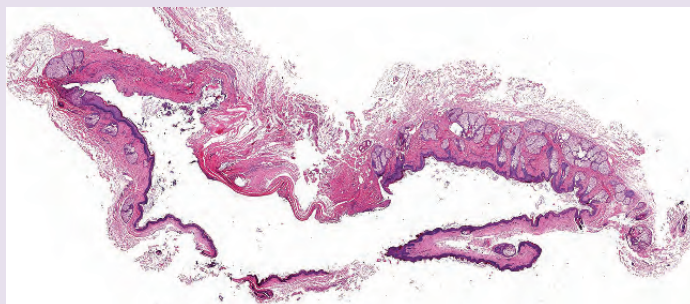
DD: Epidermoid cysts; vellus hair cysts; milia; adnexal tumors; acne.

References

- Ahn, S.K., Chung, J., Lee, W.S., Lee, S.H., and Choi, E.H. (1996) Hybrid cysts showing alternate combination of eruptive vellus hair cyst, steatocystoma multiplex, and epidermoid cyst, and an association among the three conditions. *Am J Dermatopathol* **18**(6): 645–9.
- Fernandez-Flores, A. (2015) On steatocystoma, sebaceous duct cyst, isthmic-anagenic cyst, and CK19. *Am J Dermatopathol* **37**(9): 733–4.
- Sabater-Marco, V. and Perez-Ferriols, A. (1996) Steatocystoma multiplex with smooth muscle. A hamartoma of the pilosebaceous apparatus. *Am J Dermatopathol* **18**(5): 548–50.
- Sanchez Yus, E. and Requena, L. (1990) Eruptive vellus hair cyst and steatocystoma multiplex. *Am J Dermatopathol* **12**(5): 536–7.
- Tomkova, H., Fujimoto, W., and Arata, J. (1997) Expression of keratins (K10 and K17) in steatocystoma multiplex, eruptive vellus hair cysts, and epidermoid and trichilemmal cysts. *Am J Dermatopathol* **19**(3): 250–3.

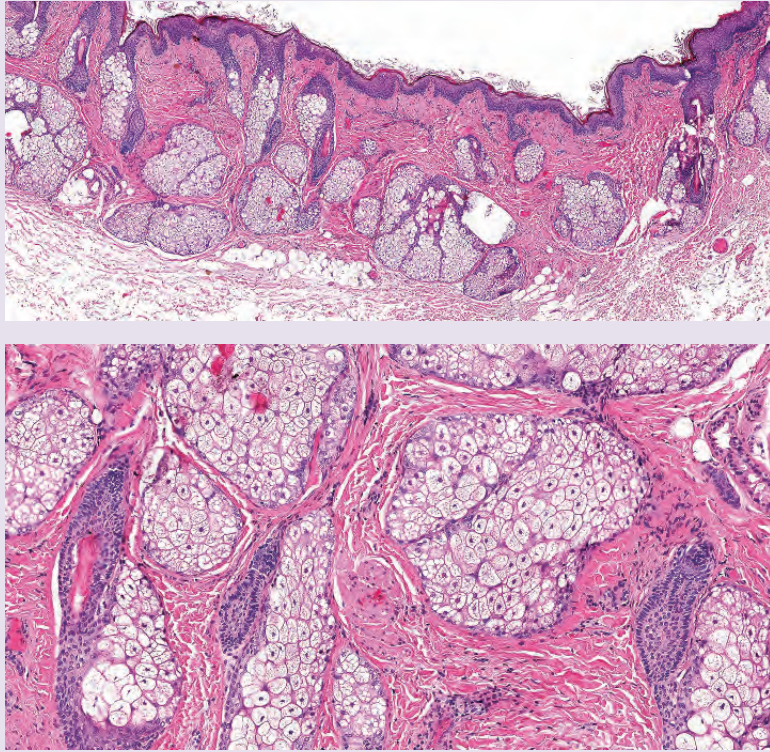
Dermoid Cyst

Cyst with
stratified
epithelium



STRATIFIED SQUAMOUS EPITHELIUM**Dermoid Cyst**

Mature epidermal appendages attached to the cyst (top and below)



This cyst develops in embryological fusion lines and contains ectodermal and mesenchymal elements. It is present from birth.

Cl: Well-defined, hard, yellow or skin-colored nodule, sometimes with vellus hairs. Preferential localisations are the periorbital and midline areas of the face.

Hi:

- Cyst wall consists of stratified squamous epithelium

- Various mature epidermal appendages such as hairs with sebaceous glands and sweat glands are attached to the cyst
 - Smooth muscle may be apparent in the cyst wall
- DD:** Epidermal cyst; steatocystoma.

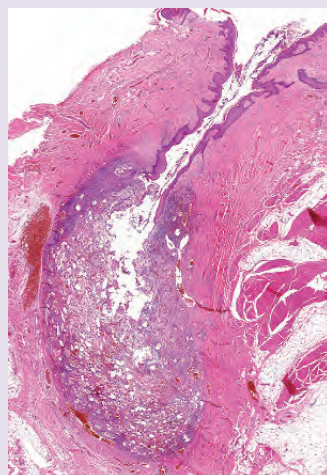
Reference

Kudo, Y., Katagiri, K., Ishii, Y., et al. (1997) Conjunctival dermoid cyst in an infant. *J Am Acad Dermatol* **36**(5 Pt 1): 784–5.

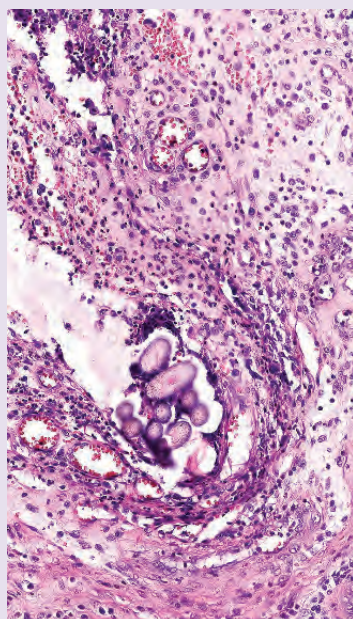
STRATIFIED SQUAMOUS EPITHELIUM

Pilonidal Sinus (Pilonidal Cyst)

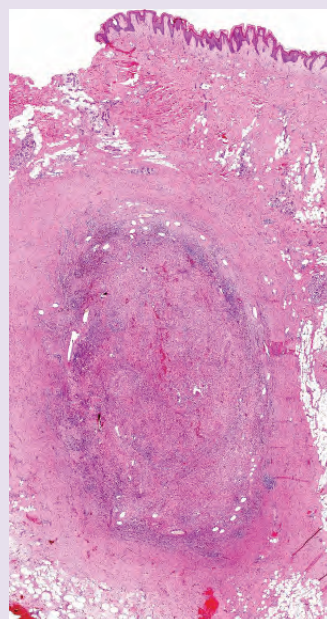
Suppurative cyst
(left), open to the
skin surface
(right)



Bottom of the
cyst, containing
debris and hairs;
granulation
tissue (left)



Obliterated cyst
with scarring
fibrosis (right)



Pilonidal sinus is part of the acne tetrad and may result from local infection and inflammation in the sacral area, corresponding to granulomatous reaction following ingrown hair of the beard. In rare cases, squamous cell carcinoma may develop within the chronic inflammatory process.

CI: The hair-bearing area in the gluteal fold is the typical localisation, where a fluctuant inflamed cystic lesion with draining to the surface develops.

Hi:

- Remnants of a ruptured epithelial cyst with stratified squamous epithelium
- Granulomatous inflammation containing multiple hair shafts without epithelial lining
- Scarring fibrosis as late-stage manifestation

DD: Other inflamed cysts; acneiform lesions.

NON-STRATIFIED SQUAMOUS EPITHELIUM

References

- Kim, Y.A. and Thomas, I. (1993) Metastatic squamous cell carcinoma arising in a pilonidal sinus. *J Am Acad Dermatol* **29**(2 Pt 1): 272–4.
- Val-Bernal, J.F., Azcarretazabal, T., and Garijo, M.F. (1999) Pilonidal sinus of the penis. A report of two cases, one of them associated with actinomycosis. *J Cutan Pathol* **26**(3): 155–8.

Non-Stratified Squamous Epithelium

Some adnexal tumors, delineated in the respective chapter, and other cysts of non-stratified squamous epithelium are not further discussed here.

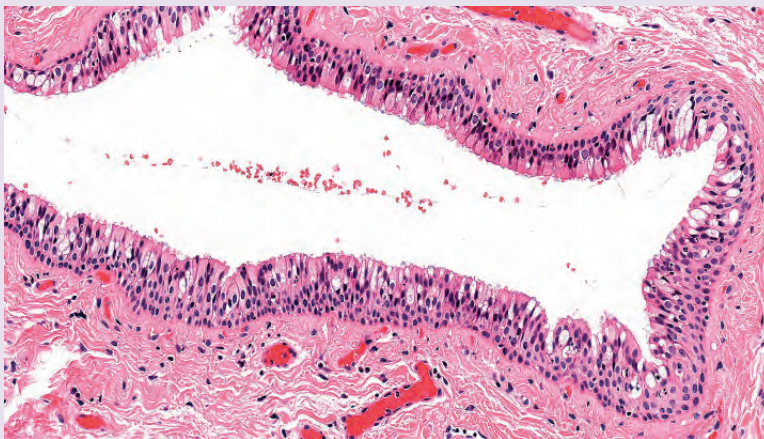
- Eccrine hidrocystoma
- Apocrine hidrocystoma

- Papillary apocrine cystadenoma
- Bronchiogenic cyst
- Branchial cleft cyst
- Thyroglossal duct cyst
- Ciliated cyst of the vulva
- Omphalomesenteric cyst
- Gartner's duct cyst
- Endometriosis

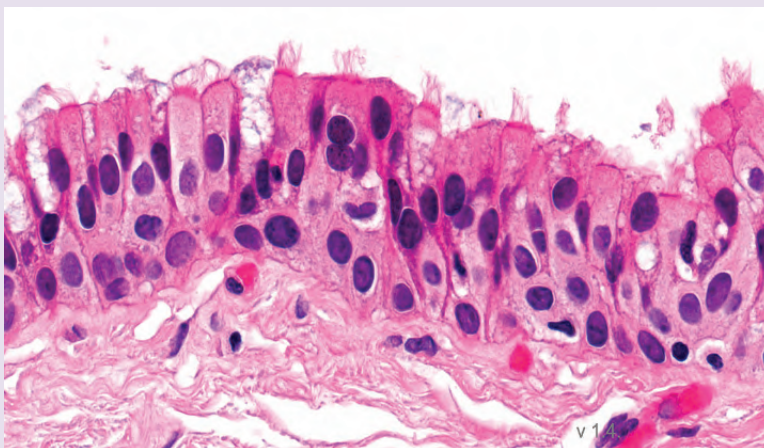
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Cutaneous Ciliated Cyst of the Lower Limb



Cyst showing cuboidal ciliated epithelium (top and bottom)



NON-STRATIFIED SQUAMOUS EPITHELIUM

Develops almost exclusively in women, originating from heterotopic tissue of the Müllerian duct and manifesting on the lower extremities. However, other locations and presentation in men also occur.

Cl: Solitary lesion presenting as subcutaneous swelling on the back or lower extremities.

Hi:

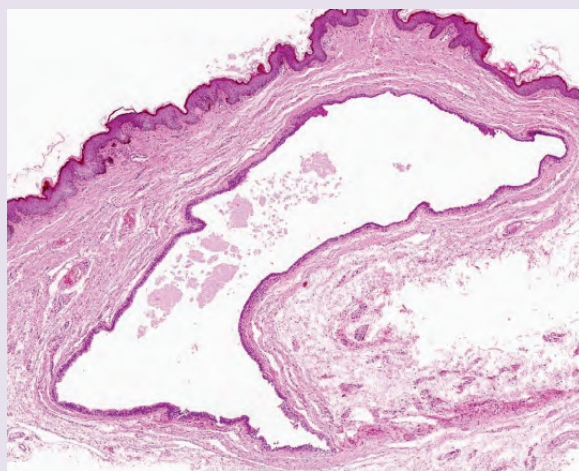
- Deep dermis or subcutis
- The cyst wall consists of cylindrical or cuboidal epithelium, lined by ciliated cells
- Cavity microscopically empty or filled with oily fluid

DD: Various cysts; apocrine hidrocystoma.

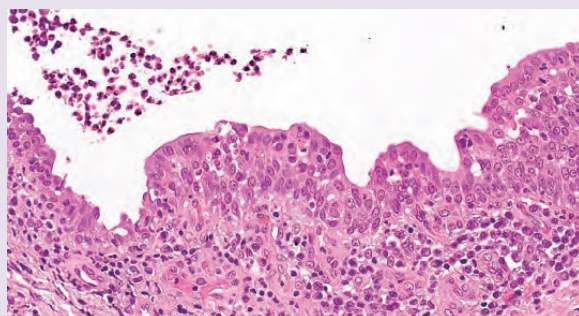
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Median Raphe Cyst



Irregularly shaped cyst with pseudostratified epithelial wall (top and bottom)



This cyst is a result of defects in embryological development of the median raphe, which extends from the urethra to the anus and normally is closed before birth.

Cl: Small translucent papules on the penis or perineum.

Hi:

- Irregularly shaped hidrocystoma-like cyst in the mid dermis
- Cyst wall lined by pseudostratified columnar epithelium
- No connection with the epidermis
- Occasionally mucin-secreting cyst wall or pigmented or ciliated

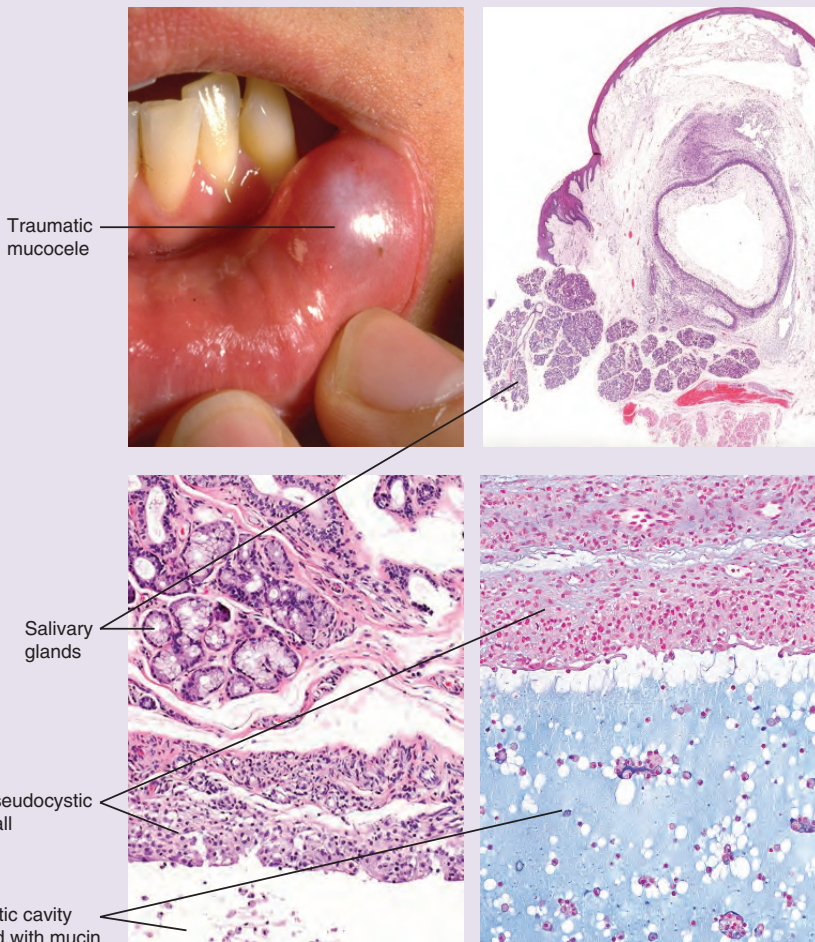
DD: Apocrine cystadenoma.

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Cysts without Epithelial Lining (Pseudocysts)

Oral Mucous Cyst and Superficial Mucocele of the Lip



Cl: Translucent submucosal node developing on lip, tongue or buccal mucosa in the vicinity of salivary glands, following minor injury.

Hi:

- Deposit of sialomucin (PAS, alcian blue), produced by salivary glands in the vicinity
- Fibrous and inflammatory reactions provide a pseudocystic wall
- Remnants of ruptured salivary duct

Reference

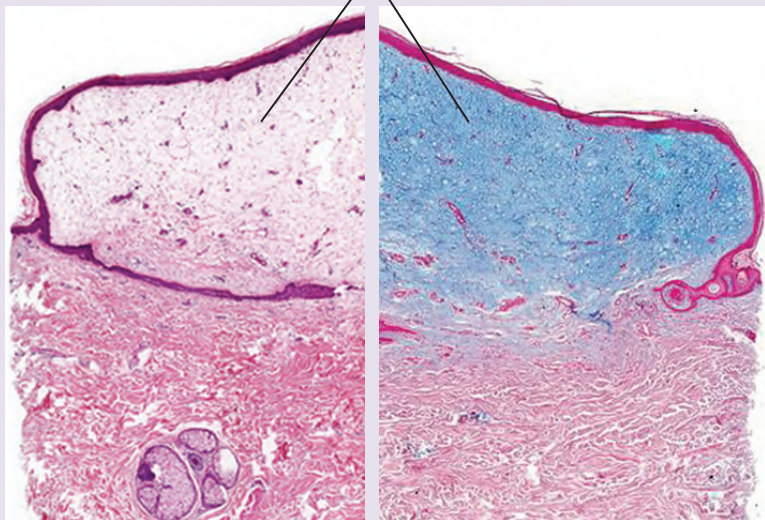
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Digital Myxoid Cyst

Cyst over distal interphalangeal joint



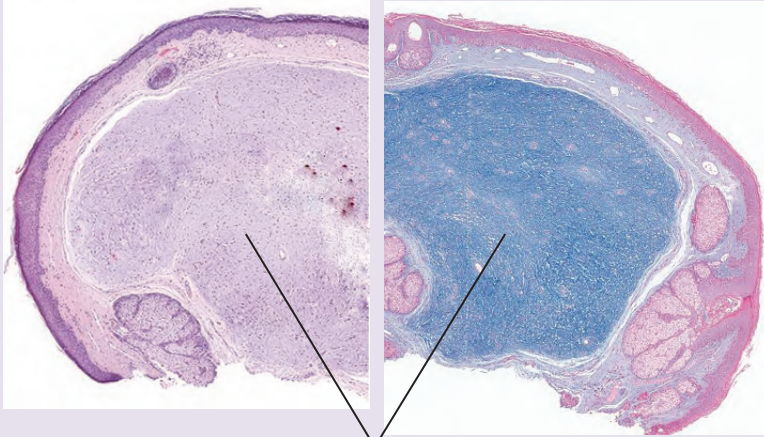
Mucin deposits (HE, alcian blue)



This cyst is considered to be either a variant of a ganglion connected with an interphalangeal joint

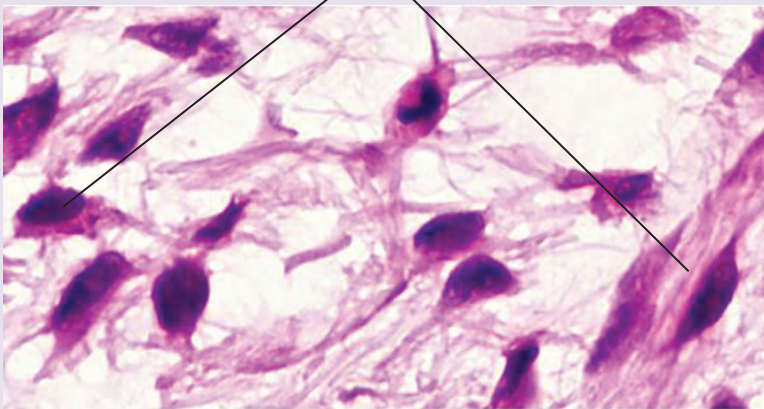
or resulting from independent proliferation of fibroblasts, producing glucosaminoglycans.

DD of Digital Myxoid Cyst: Cutaneous Myxoma



Well-defined, circumscribed, unencapsulated mucin deposits (HE, alcian blue)

Spindle-shaped and dendritic fibroblasts



Cl: Translucent small cysts over the dorsal aspects of interphalangeal joints, preferentially of the fingers.

Hi:

- Very thin (“membranous”) overlying epidermis
- No cyst wall
- Mucinous deposits within the dermis
- Lack of vessels within mucinous zones
- Occasionally, histiocytic or granulomatous inflammatory response along with a fibrous pseudocapsule

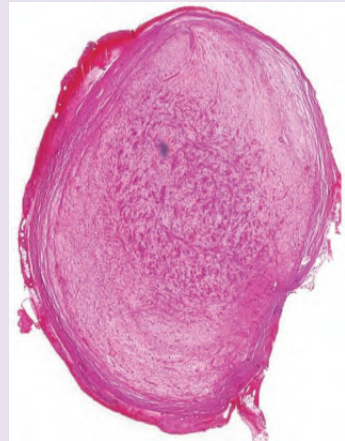
DD: Cutaneous myxoma; wart; digital fibrokeratoma; digital synovial cyst (ganglion).

Reference

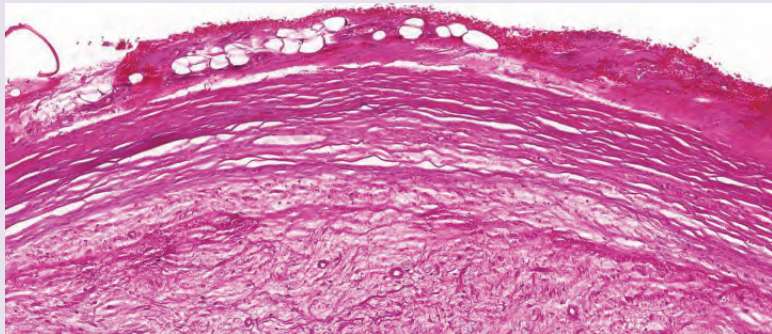
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Synovial Cyst (Ganglion)

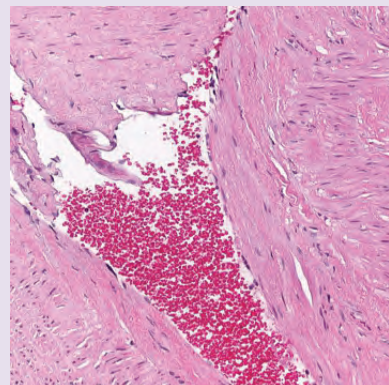
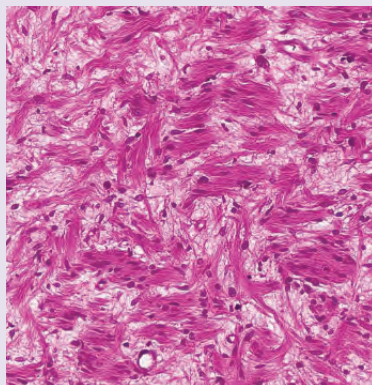
Firm node on the wrist of one hand (left and right)



Pseudocystic wall formed by fibrous myxoid tissue (mid and bottom left)



Synovia of the joint (right)



Cl: Small pseudocyst, often preceded by trauma.
Location: extremities, near joints.

Hi:

- Wall formed by fibrous tissue
- Connection with the synovia of the underlying joint
- Amorphous myxoid material in the cystic cavity
- Fibrous scar formation

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